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Review

Regulation of signaling pathways by tanshinones in different cancers

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Abstract: Past several years have witnessed dramatic leaps in our understanding of rewiring of gene expression at the translation level during cancer developmentthat provides linchpin support to the transformed phenotype. Most recent and ground-breaking developments in the field of molecular oncology aredriven by an explosion in technological advancements and have started to reveal previously unimagined regulatory mechanisms and how they intricately co-ordinate to modulate cancer progression, loss of apoptosis and development of resistance against different therapeutics. However, the insights gained from work in this natural product research have far-reaching impact because of rapidly increasing repertoire of medicinally and biologically efficient phytochemicals. How Tanshinones mediate targeting of JAK-STAT, ER stress associated signaling cascade,PI3K/AKT/mTOR pathway,autophagy, TRAIL pathway and microRNAs are being discovered and will prove to be helpful in getting a step closer to personalized medicine.

Key words: TRAIL; Cancer; Tanshinones; Signaling; Apoptosis.

Introduction

Currently, majorstumbling blocks with regard to the efficacy and safety of therapeutic interventions against cancers are off-target effects, rapidly developing resistance against multiple drugs, a situation that largely reflects the genetic/epigenetic mutations, intra and inter-tumor heterogeneity of cancer cells (1,2,3). Data obtained through high-throughput technologies provided evidence that even within a single genotype, each individual cancer cell possessedhighly variant gene expression levels, phenotypes and characteristically unique features (4,5).We have entered into an exciting era where the ancient wisdom distilled into the world's natural products can be re-interpreted and therapeutically utilized through the lens of modern science (6).Tanshinones are lipo-soluble components of Tanshen and compose of abietane type-diterpenequinone pigments. Primary bioactive constituents among the tanshinones are tanshinone I, tanshinone IIA and cryptotanshinone, which have gained significant appreciation because of their ability to target wide ranging proteins in different cancers.

In this mini-review we have attempted to summarize emerging trends and exciting new discoveries that reveal how Tanshinones effectively modulated different signaling cascades in different cancers, regulation of microRNAs and TRAIL pathway by these wonderful natural products. Following section deals with JAK-STAT signaling cascade and how Tanshinones regulate this pathway.

JAK-STAT pathway

CD4+/CD8+ T cells were treated with 10µM concentration of cryptotanshinone for 48 hours (7). Cryptotanshinone treatment markedlyenhanced the cytotoxicity of the $CD4^+$ T cells. However, cryptotanshinonedid not exert effects on cytotoxicity of the $CD8^+$ T cells. Cryptotanshinone significantly increased the p-JAK2 and p-STAT4 of the $CD4^+$ T cells (7).

It has been shown that chemokine (C-C motif) ligand 2 (CCL2) mediated pathway played an instrumental role in STAT3 activation and epithelial-mesenchymal transition (EMT) in bladder cancer cells (8). Tanshinone IIA exerted inhibitory effects on STAT3 activation by reducing STAT3 phosphorylation at 705^{th} tyrosine residue in bladder cancer cells. STAT3 inhibition resulted in the inhibition of CCL2 expression. Data clearly revealed that Tanshinone IIA downregulated CCL2 expression mainly through STAT3 inhibition in bladder cancer cells (8). In the upcoming section we discuss how ER stress is modulated by Tanshinones in different cancers.

ER stress

Data obtained through advanced technologies has helped us to understand how endoplasmic reticulum (ER) stress initiates characteristically distinct signaling pathways (9).When the cells are under ER stress, activation of different well-orchestrated processes takes place to restore ER homeostasis.When the load of misfolded proteins gets higher, the unfolded protein response (UPR) initiates with the activation of 3 trans-membrane effectors: eukaryotic translation initiation factor 2α kinase-3 (PERK), activating transcription factor-6 (ATF6) and serine/threonine-protein kinase/endoribonuclease IRE1 (IRE1) (9, 10).

Tanshinone-IIA significantly enhancedBiP/GRP78 in LNCaP cells. There was a marked increase in the expression of IRE1-a, but the levels of p-eIF-2a and ATF6 remained unchanged in prostate cancer cell lines (11). IRE1-aupregulation was notable as early as 3 hours(1.48-folds) and increased till 48 hours (2.13-folds). IRE1-a upregulation in PC-3 cells was noticeable after 12 hours (1.3-folds). Tanshinone -IIA-mediated increase in the expression of GADD153/CHOP was 8.9- and 12.1-folds after 48 hours in treatedPC-3 and LNCaP cell lines. There was a dose-dependent increase in the expression ofGADD153/CHOP, BiP and IRE1-ain Tanshinone -IIA treated LNCaP cells. Translocation of GADD153/CHOP into nucleus was indicative of astress induced signaling pathway in the nucleus. At 12 hours, GADD153/CHOP appeared to bein abundance in the nuclei of PC-3 and LNCaP cells treated with Tanshinone –IIA (11).

Tanshinone IIA induced an increase in protein levels of PKR-like endoplasmic reticulum kinase (PERK), activating transcription factor-6 (ATF6) and C/EBP Homologous Protein (CHOP) to induce endoplasmic reticulum-associated stress and apoptotic death in pancreatic cancer BxPC-3 cells (shown in figure 1) (12). Tanshinone IIA considerably enhanced formation of autophagic bodies in A375 cells. Tanshinone IIA dose dependently enhanced protein levels of autophagy-associated genes (13).

PI3K/Akt/mTOR/p70S6K1

Tanshinone IIA significantly reduced protein phosphorylation of PI3K, pAkt, phosphorylated-mammalian target of rapamycin (p-mTOR) and phosphorylated-p70 ribosomal protein S6 kinase-1 (p70S6K1). Interestingly, higher concentrations significantly reduced phosphorylation of different proteins (13). These findings provided evidence that Tanshinone IIA regulated autophagic production, LC3-II, Beclin-1 and PI3K/Akt/mTOR/p70S6K1 signal transduction cascade in A375 cell line (13).

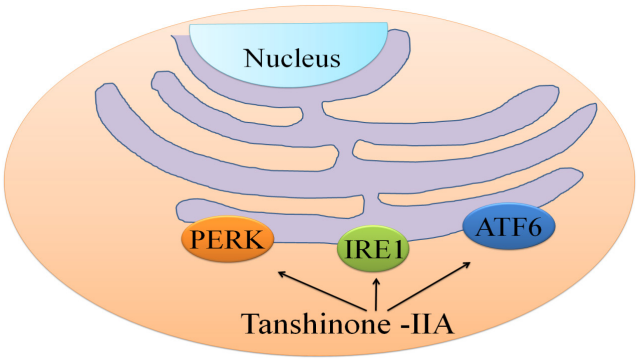

Figure 1. shows Tanshinone mediated regulation of ER Stress pathways.

Tanshinone IIA considerably reduced phosphorylated levels of PI3K and Akt proteins, inhibited cell viability and induced apoptotic cell death in U251 glioma cells (14).

TanshinoneI mediated effects on Akt/PKB and related downstream effectors of Akt signaling cascade (PI3K, p-PI3K, Akt, p-Akt, mTOR and p-mTOR) were investigatedby the use of phosphorylated antibodies specific to Akt, mTOR and PI3Kbyimmunoblot assay (15). Computer-assisted image analysis revealedthat TanshinoneI dose-dependently reduced phosphorylation of Akt at 308th threonine residue and PI3K in MCF-1 and MDA-MB-453 cells. Interestingly, levels of total Akt and PI3K remained unchanged by Tanshinone I under similar conditions. Tanshinone Idose-dependently increased dephosphorylated form of mTOR in the MDA-MB-453 and MCF-7 breast cancer cells. Findings clearly suggested that Tanshinone I-induced growth inhibitory effects wereexerted by PI3K/Aktpathway inactivation in breast cancer cells (15).

FOXM1

Tanshinone IIA dose-dependently reduced Forkhead Box M1 (FOXM1) in SGC-7901 cells (16). Detailed mechanistic insights revealed that FOXM1 inhibition had similar effects as Tanshinone IIA on SGC-7901 cells and FOXM1 overexpression partially impaired Tanshinone IIA mediated inhibitory effects on proliferation and migration of SGC-7901 cells (16).

Mitogen Activated Protein Kinases

Increasingly it is being realized that functionalities ofJNKs and p38 MAPKs in carcinogenesis are intricate,which is consistent with the wide-ranging cellularresponses that they modulate (17, 18). Cancer cells have the ability to subvert these pathways to facilitate survival, proliferationand invasion (17, 18).

Dihydrotanshinonedose dependentlyincreased the phosphorylation of c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK)in both MGC803 and SGC7901 cells (19). There was an increase in the phosphorylated levels of JNK and p38 by 0.52- and 2.68-fold respectivelyin SGC7901 cells treated with 6 μM dihydrotanshinone for 24 hours. Activation of p38 phosphorylation occurred within 30 minutes in both MGC803 and SGC7901 cells. JNK/p38 signaling cascade in MGC803 cells was more sensitive towards dihydrotanshinone as compared to SGC7901 cells (19).

Regulation of autophagy by tanshinones

Microtubule-associated protein 1A/1B-light chain 3 (LC3), an autophagosome structural LC3 protein interacted with multiple cargo receptors through their LIR domains. Tanshinone IIA promoted autophagy in U251 glioma cells and upregulated LC3B and Beclin

1(20).LC3II/LC3I levels give a clue of the degree of autophagy. Detailed structural studies revealed that Beclin-1 was instrumental in orchestration of cytoprotective functions of autophagy and in opposing apoptotic cell death (21). Inhibition of autophagy at the final degradation phase resulted in an elevation of the LC3II/LC3I level. CQ (autophagy inhibitor) pharmacologically blocked fusion of autophagosome lysosomes and sequestrated autophagosomes to inhibit autophagic flux. Beclin-1 and LC3II/LC3I levels were upregulated after treatment with CQ. Modest increase in cleaved-PARP, LC3II/LC3I and caspase-3 was evident in cells combinatorially treated with 2.5 mg/l Tanshinone IIA and CQ as compared to Tanshinone IIA alone. There was a reduction in the quantities of cleaved-caspase-3 and cleaved-PARP but an increase in LC3II/LC3I was noted in osteosarcoma MG-63 cells treated with a high dosage of Tanshinone IIA and CQ as compared to a high dosage of Tanshinone IIA (5 and 10 mg/l) alone. Cytoprotectiverole of autophagy was noted inMG-63 cells but afterwards, because of an excessive damage to the cells and accumulation of intracellular levels of reactive oxygen species (ROS), protective autophagy sequentially shifted to autophagic cell death involved in apoptosis (21).

Tanshinone I markedly enhanced the LC3I to LC3II-conversion and triggered autophagosomal formation, however, Beclin-1expression remained unchanged (22). B-cell lymphoma-2 (Bcl-2), an anti-apoptotic protein negatively modulated autophagy by binding to Beclin-1 and disruptedstructural association between VPS34 and Beclin-1. Dissociation of Beclin-1 and VPS34 promoted homo-dimerization of Beclin-1 and inhibition of autophagosomal formation. Tanshinone I induced an increase in Beclin-1-VPS34 complexes and inhibited Bcl-2 expression (22). Bcl-2 overexpression induced an increase in Beclin-1/Bcl-2 complex because of disassembly of VPS34/Beclin-1 complexwhich consequently inhibited autophagosomal formation. Tanshinone I-induced apoptosis was more pronounced in ATG7 silenced BGC823and SGC7901 cells (22).

Matrix metalloproteinases

Tanshinone IIA (1.0 mg/mL) exerted inhibitory effects on invasion and metastasizing potential of SW620 cells. E-cadherin was significantly increased and levels of MMP-9 and vimentin were significantly decreased after treatment with Tanshinone IIA for 24 hours (23).

Tanshinone II-A exerted inhibitory effects on in-vitro and in vivo invasion and metastatic spread of colorectal cancer cells by reducing levels of MMP-2 and MMP-9 and urokinase plasminogen activator (uPA) (24). Tissue inhibitor of matrix metalloproteinase proteins (TIMPs) restricted aberrant motility and invasion by protecting cell adhesion molecules (integrins and cadherins) from protease cleavage and by simultaneous inhibition of MMP-dependent degradation of the structural matrix. Furthermore, Tanshinone II-A increased levels of TIMP-1 and TIMP-2 in treated cancer cells (24). Tanshinone II-A decreased MMP-2, -7 and -9 in gastric AGS cancer cells (shown in figure 2) (25). Transfection of Collagen XVI overexpressing OSCC cell clones with vectors containing different fragments of MMP9 promoter region adjacently located to a luciferase reporter demonstrated a gradual enhancement in luciferase signals (26). Intriguingly, deleting the activator protein 1 (AP-1) binding site located upstream of the reported transcriptional start site transcriptionally downregulated the expression of MMP9. Similar results were obtained upon Tanshinone IIA mediated targeting of AP-1 in cancer cells (26).

TRAIL pathway

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has emerged as one amongst the most deeply studied therapeutically beneficial molecules having remarkable anticancer activity (27). TRAIL based therapies have entered into various phases of clinical trials because of commendable ability of TRAIL to selectively target cancer cells and leaving normal cells intact. TRAIL transduced the signals intracellularly through death receptors (DR4 and DR5) (27).

There are direct pieces of evidence which highlight the role of CHOP in transcriptional upregulation of DR5 in cancer cells. Azadirone, a limonoidtetranortriterpene and quercetin have previously been tested as TRAIL sensitizers and these natural products efficiently induced apoptosis in TRAIL-resistant cancer cells via upregulation of DR5 (28, 29).

Tanshinone IIA sensitized NSCLC cells to TRAIL mediated apoptosis. Tanshinone IIA treatment significantly increased DR5 in A549, H1299 and H596 cells (30). Tanshinone IIA dose-dependently induced transcriptional upregulation of CHOP and DR5 (30). Survivin is an anti-apoptotic protein which negatively regulated TRAIL induced apoptosis (31). Tanshinone IIA enhanced TRAIL induced molecular effects via downregulation of survivin in ovarian carcinoma cells (shown in figure 1) (31). Tanshinone IIA concentration-dependently upregulated DR5 protein and mRNA expression in SKOV3 and TOV-21G (31). Detailed mechanistic insights revealed that Tanshinone IIA promoted JNK-mediated signaling to upregulate CHOP which consequently induced expression of DR5. However, chemical inhibition of JNK strongly repressed Tanshinone -induced activation of CHOP and DR5 (32). Next we summarize how Tanshinones regulate expression of different microRNAs. Although, reported evidence is not detailed, however, it still gives an idea of potential of Tanshinones to regulate

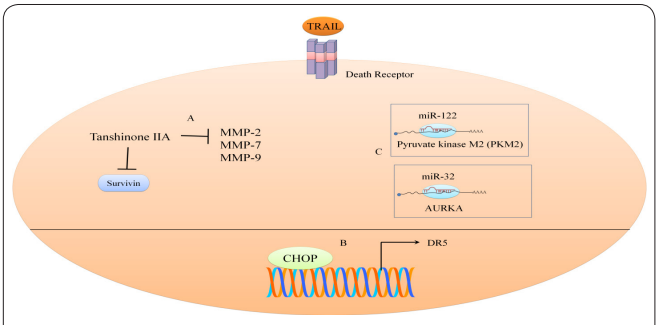

Figure 2. shows Tanshinone mediated regulation of (A) TRAIL mediated pathway. Tanshinone inhibited survivin, MMPs in cancer cells. (B) CHOP mediated transcriptional upregulation of DR5 to sensitize TRAIL-resistant cancer cells to TRAIL based therapeutics. (C) microRNA regulation of different genes is shown in the figure. Tanshinone was noted to increase the expression of these miRNAs.

oncogenic and tumor suppressor miRNAs.

Tanshinones mediated microRNA regulation

Tanshinones upregulated miR-137expression as evidenced by higher expression of miR-137 in H1299 cells. Tanshinone mediated effects were impaired when cells were transfected with miR-137 inhibitor(shown in figure 2)(33). Tanshinone IIA-induced upregulation of miR-122 in Ec109 cells. Tanshinone IIA inhibited proliferation through miR122-mediated targeting of Pyruvate kinase M2 (PKM2) (34).Aurora A (AURKA), a serine-threonine kinase is responsible for regulation of mitotic processes in cells, including centrosomal maturation, spindle assembly and chromosomal segregation (35). Tanshinone I (4 μM), Tanshinone IIA (4 μM) or cryptotanishone (5 μM) significantly reduced mRNA and protein levels of AURKA in H1299 cells. Tanshinones triggered upregulation of miR-32 in H1299 cells and miR-32 directly targeted AURKA in H1299 cells (35).

Protein-tyrosine phosphatases are highly pleomorphic set of proteins involved in regulation of cellular response to extracellular signals (36). Protein-Tyrosine Phosphatase Nonreceptor-Type-11 (PTPN11) is critically involved in post-translational modifications of different proteins. SHP2 is the protein encoded by PTPN11 and involved in regulation of different proteins. Tanshinone IIA (80 μM) upregulated PTPN11 in Hep3B cells. PTPN11 (1.2-fold) was maximally induced in Hep3B cells treated with 80μM of Tanshinone IIA. SHP2 was notably enhanced in Hep3B cells treated with Tanshinone IIA. p53 binding toa specific PTPN11 sequence was noted in Hep3B cells treated with 80μM of Tanshinone IIA.TanshinoneIIA directly suppressed miRNA-30b and indirectly upregulated expression of p53. Data clearly suggested that miR-30b-p53 and PTPN11/SHP2 played central role in Tanshinone IIA mediated cancer inhibitory effects (36).

Nanotechnological strategies to deliver tanshinones

Different delivery systems are currently being tested for efficacy to deliver therapeutic agents to the target sites (37). Conjugate of gold/polyethyleneimine (Au-NPs/PEI) nanoparticles and sulphated β-cyclodextrin (CD) efficiently delivered Tanshinone IIA to prostate cancer PC-3 and DU145 cells (37).Tanshinone nanoemulsion dose dependently upregulated p-JNK, p53 and p21 and downregulated cyclin D1, cyclin E1 and CDK2 expression levels in lung cancer A549 cells (38).

mPEG-PLGA-PLL-cRGD (methoxy polyethylene-glycol, polylactic-co-glycolic acid, poly-L-lysine, cyclic arginine-glycine-aspartic acid) NPs are considered as promising delivery systems. In accordance with this approach, Tanshinone IIA was loaded into mPEG-PLGA-PLL-cRGD NPs and tested for efficacy against hepatocellular carcinoma cells (39). Tanshinone IIA loaded NPs were stable and uniformly distributed, extended release-time and improved tumor-targeting activity (39).

Glycyrrhetinic acid coupling PEG-disulfide linkage-poly(lactic-co-glycolic acid) (GA-PEG-SS-PLGA) has emerged as a prominent delivery system because of hepatoma-targeting and redox-responsive release of the drug (40). GA-decorated micelles were internalized by HepG2 cells mainly through micro-pinocytosis and caveolae-mediated endocytosis. Tanshinone IIA-loaded micelles demonstrated better bio-availability, extended circulation time and accumulated efficiently in the liver. GA-PEG-SS-PLGA micelles loaded with Tanshinone IIA considerably repressed growth of the tumor and enhanced survival time in xenografted mice (40).

Focus of the upcoming section is particularly on the updates related to Tanshinones mediated tumor suppressive effects in xenografted mice.

Preclinical studies

Tumor growth was considerably reduced in mice subcutaneously injected with Tanshinone IIA (20 mg/kg) (41). Micro-vessel density in the tumor was markedly reduced in the Tanshinone IIA treated mice. Surprisingly, tumor metastasis was not detected in the mice injected with osteosarcoma 143B cells, which differed from the findings obtained from in-vitro assays associated with migration and invasion. Injection of 143B cells onto subcutaneous tissues instead of bone marrow might be the reason for such a response which needs further research (41).

Tanshinone IIA was intraperitoneally injected for 8 weeks in SCID mice xenografted with AGS cells (42). Results revealed that Tanshinone IIA significantly inhibited tumor growth in xenografted mice. Tanshinone IIA dose dependently decreased EGFR, IGFR, PI3K, AKT, mTOR in tumors (42).

Acetyltanshinone IIA (ATA), a chemically modified form of tanshinone IIA was found to be effective against breast cancer cells (43). ATA downregulated cellular levels of HER2 and Epidermal Growth Factor Receptor (EGFR) in SK-BR-3 and MDA-MB-453 cells. More importantly, ATA dose- and time- dependently reduced phosphorylation/activation of these proteins. There was a significant reduction in tumor volume and tumor weight in mice administered with ATA (5 mg/kg)3 times/week. There was an increase in the average volume of tumors from 95.79 ± 12.02 mm^3 to 285.27 ± 25.24 mm^3 in the negative control group. However, average volume of tumors reduced from 99.55 ± 11.13 mm^3 to 46.49 ± 10.20 mm^3 in xenografted mice administered with ATA (43).

Tanshinone IIA concentration dependently induced considerable decrease in volume of the A375 cell transplanted skin melanoma tumors (13). Furthermore, at 28th day, Tanshinone IIA (25 μg/g), paclitaxel (8 μg/g) or Tanshinone IIA (50 μg/g) treatments induced significant reduction in weights of A375 cell transplanted skin melanoma tumors. Significantly smaller tumor sizes were noted in mice treated with Tanshinone IIA (25 μg/g), paclitaxel (8 μg/g) or Tanshinone IIA (50 μg/g) (13).

Western blot and immunofluorescence assays revealed that TGF-β1 treatment induced an increase in the levels of β-catenin, T-cell factor (TCF3) and lymphocyte enhancement factor (LEF1) and these effects are inhibited by Tanshinone IIA (44). TCF3/LEF1 and β-catenin are reduced in Tanshinone IIA-treated hypoxic HT-29 cells. Similarly, promoter activity of TCF/LEF

is notably repressed in Tanshinone IIA-treated hypoxic HT-29 cells. Tanshinone IIA loaded mesoporous silica nanoparticles markedly reduced tumor growth in mice subcutaneously transplanted with fluorescence-labeled HT-29/HIF-1$\alpha^{+/+}$ cells (44).

Conclusion

Better understanding of how natural products efficiently targeted signaling pathways in different cancers and exploration of new ways to harness plant chemodiversity for medicinal uses hence offered a gate-way to a new era of systems-level and individualized medicine havingconsiderablepotential to advance human health. Overwhelmingly increasing cellular and pre-clinical findings have considerably expanded the field of molecular oncology. Tanshinones have attracted appreciation because of their ability to suppress cancer development, metastatic spread and target multiple oncogenic cell signaling pathways. Tanshinones have been shown to effectively modulate JAK-STAT pathway, TRAIL mediated pathway, microRNAs, PI3K/Akt/mTOR transduction cascade to inhibit or suppress cancer. However, we still have insufficient information about the regulation of Notch pathway by Tanshinones. How Tanshinones modulate TGF/SMAD pathway is also an understudied area. Better understanding of these aspects will prove to be helpful in getting a step closer to individualized medicine.

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