

MINI-REVIEW

Dealing Naturally with Stumbling Blocks on Highways and Byways of TRAIL Induced Signaling

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Abstract

In-depth analysis of how TRAIL signals through death receptors to induce apoptosis in cancer cells using high throughput technologies has added new layers of knowledge. However, the wealth of information has also highlighted the fact that TRAIL induced apoptosis may be impaired as evidenced by experimental findings obtained from TRAIL resistant cancer cell lines. Overwhelmingly, increasing understanding of TRAIL mediated apoptosis has helped in identifying synthetic and natural compounds which can restore TRAIL induced apoptosis via functionalization of either extrinsic or intrinsic pathways. Increasingly it is being realized that biologically active phytochemicals modulate TRAIL induced apoptosis, as evidenced by cell-based studies. In this review we have attempted to provide an overview of how different phytonutrients have shown efficacy in restoring apoptosis in TRAIL resistant cancer cells. We partition this review into how the TRAIL mediated signaling landscape has broadened over the years and how TRAIL induced signaling machinery crosstalks with autophagic protein networks. Subsequently, we provide a generalized view of considerable biological activity of coumarins against a wide range of cancer cell lines and how coumarins (psoralidin and esculetin) isolated from natural sources have improved TRAIL induced apoptosis in resistant cancer cells. We summarize recent updates on piperlongumine, phenethyl isothiocyanate and luteolin induced activation of TRAIL mediated apoptosis. The data obtained from pre-clinical studies will be helpful in translation of information from benchtop to the bedside.

Keywords: TRAIL - apoptosis - coumarin - piperlongumine - signaling

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Introduction

Decades of research in molecular oncology have convincingly revealed many of the details that have helped us in developing a deeper understanding of molecular basis of cancer. *In vitro* studies have shown that genetic/epigenetic mutations, overexpression of oncogenes, inactivation of tumor suppressor genes, dysregulation of spatio-temporally controlled intracellular signaling cascades and imbalance of pro-apoptotic and anti-apoptotic proteins are some of the deeply studied mechanisms.

It is becoming increasingly recognized that cell death is a biological mechanism that is highly branched network of proteins which are orchestrated and tightly regulated. High-throughput technologies have helped in identification of molecular composition of caspase-8 activation platform and it is now known that a signalosome

is formed at death receptor consisting of FADD, pro-caspase-8 and death receptor. This multiprotein complex is termed as Death Inducing Signaling Complex. (DISC). Laboratory methodologies have added new information into the biology of extrinsic and intrinsic signaling pathways. Extrinsic pathway operates through caspase-8 mediated activation of caspase-3. Intrinsic pathway is functionalized through caspase-8 mediated cleavage of BH3-only protein Bid. Mitochondrion has been noted to be a central regulatory node in modulation of intrinsic pathway as evidenced by efflux of cytochrome-c, Omi/Htra, SMAC/DIABLO upon entry of Truncated Bid. Both Smac and Htra2 take part in neutralizing the anti-apoptotic functions of the inhibitor of apoptosis proteins (IAPs). Cytochrome C, APAF and Pro-caspase-9 form a multiprotein complex termed as apoptosome. Activated caspase-9 further activated caspase-3 (van Roosmalen et al., 2014).

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Crosstalk between TRAIL Induced Signaling Machinery and Autophagic Molecular Network

Increasingly it is being realized that autophagy associated proteins positively and negatively regulate TRAIL induced apoptosis. Basal levels of autophagosomes were noted to be considerably higher in TRAIL resistant breast cancer cells. Comparative analysis of TRAIL sensitive and resistant breast cancer cell lines revealed marked difference in cell surface expression of receptors for TRAIL. Death receptors for TRAIL have been experimentally verified to co-localize with LC3-II within autophagosomes in cancer cells Di et al (2013). It is noteworthy that TRAIL induced autophagic response in cancer cells exerted mechanistically divergent effects. TRAIL treated ATG7 silenced papillary thyroid cancer cells did not undergo apoptosis. Contrary to this, TRAIL treated ATG7 silenced anaplastic thyroid cancer cells revealed a greater apoptotic rate Jin et al (2014). There is a direct piece of evidence suggesting that anti-apoptotic proteins including BCL2 and BCL2L1/BCL-xL negatively regulate autophagy via interacting with BECN1. In depth in-vitro evidence revealed that MAPK8 was activated in TRAIL treated cancer cells and targeted inhibition of MAPK8 protected BCL2L1/Bcl-xL from degradation thus stabilizing BCL2L1-BECN1 complex He et al (2012). Beclin has also been shown to interact with survivin to impair TRAIL induced apoptosis Niu et al (2010).

All these pieces of information have added another layer of complexity regarding context dependent interplay of autophagy associated proteins in cancer cells. Decreasing the number of available death receptors and modulation of TRAIL induced apoptosis via autophagy needs deeper research in different cancer cells. More specifically, natural agents must be combined with TRAIL to note the efficacy and autophagic response in cancer cells. Moreover, how natural agents modulate miRNA subsets to regulate autophagic response has also gained appreciation and currently under investigation. Data obtained from cell culture studies and xenografted mice will be helpful in developing a better understanding of autophagic response in different cancers.

There is a list of newly emerging scientific evidence highlighting molecular mechanisms to enhance or restore TRAIL induce apoptosis in cancer cells (Zhao et al., 2011; Huang et al., 2012; Jiang et al., 2013; Silva et al., 2014). Wide ranging phytochemicals are currently being tested for efficacy. The results obtained are encouraging and need further testing in xenografted mice. Details can be found elsewhere (Aras et al., 2014; Sehitoğlu et al., 2014).

Coumarins

Diversin is prenylated coumarin with notable biological activity. It exerted its effects via functionalizing caspase-3 in bladder cancer cells. Additionally, growth interest was noted in Diversin treated bladder cancer cells (Haghighitalab et al., 2014). Similar research group reported considerable biological activity of

7-isopentenylcoumarin against bladder cancer cells (Haghighi et al., 2014).

Imperatorin is a fuco-coumarin isolated from *Angelica dahurica* reported to activate extrinsic and intrinsic pathways. It was observed that Imperatorin induced degradation of anti-apoptotic protein, Mcl-1 and considerably reduced tumor growth in xenografted mice (Li et al., 2014). There is a direct piece of experimentally verified evidence identifying that coumarin-3-carboxylic acid in combination with valproic acid worked with effective synergy. Drug treated cancer cells indicated a marked decrease in protein levels of NF- κ B, cyclin D1 and Bcl-2. It is also worth describing that growth factor mediated intracellular signaling was also inhibited as evidenced by significant reduction in phosphorylated levels of c-Met, VEGFR2 and EGFR (Liu et al., 2013).

Coumarin-chalcone hybrids have tested for efficacy in cell culture studies. Mitochondrial pathway was noted to be activated in drug treated cancer cells. It is noteworthy that orally administered Coumarin-chalcone hybrids significantly inhibited tumor development in SCID mice xenografted with HeLa cells (Singh et al., 2014). In line with similar approach, 6-brominated coumarin hydrazide-hydrazone derivatives (BCHHD) have also emerged as potent inducers of apoptosis in pancreatic carcinoma (Panc-1) cells. *In vitro* assays revealed that BCHHD induced expression of CDKN1A, GDF-15 and DDIT4. Moreover, CDC2, CDC20, CDK2 genes were markedly downregulated (Nasr et al., 2014). Certain hints have emerged highlighting role of coumarin analogs in the targeting of angiogenesis. Coumarin analogs exerted inhibitory effects on angiogenesis in mice bearing either Daltons lymphoma ascites or Ehrlich ascites carcinoma cells (Vijay Avin et al., 2014). coumarin-quinone derivative SV37 has been shown to considerably inhibit CDC25 phosphatase in different cancer cells (Bana et al., 2013).

Scoparone is a 6,7-dimethoxycoumarin isolated from *Artemisia capillaris* with potential activity against DU145 prostate cancer cells. Scoparone treated cancer cells displayed a marked decrease in pSTAT3 levels and its redistribution in nucleus that consequently inhibited transcriptional inhibition of its target genes (Kim et al., 2014). 5,7-dihydroxy-4-methyl-6-(3-methylbutanoyl)-coumarin (DMAC) is a coumarin derivative noted to be effective against colon cancer HCT116 and LoVo cells. Mechanistically it was revealed that DMAC exerted its effects via c-Jun N-terminal protein kinase (JNK). Targeted inhibition of JNK dramatically impaired DMAC induced apoptosis (Lin et al., 2014). Umbelliprenin, a prenylated compound has considerable anticancer activity against Jurkat T-CLL cells. It activated extrinsic and intrinsic pathways and Bcl-2 was also markedly inhibited (Gholami et al., 2013). Dentatin is a coumarin isolated from *Clausena excavata* Burm. f with notable activity against PC-3 and LNCaP prostate cancer cells. Dentatin induced activation of intrinsic pathway and expression levels of survivin, Bcl-2 and Bcl-xL were reduced (Arbab et al., 2012). In the upcoming section we discuss two examples of coumarin reported to trigger TRAIL induced apoptosis.

Esculetin is a 6,7-dihydroxycoumarin reported to effectively inhibit Wnt induced intracellular signaling in cancer cells as evidenced by direct binding of chemical with the Asn387, Gly307, Lys345, and Lys312 residues of β -catenin in colon cancer cells (Lee et al., 2013). Esculetin treated oral cancer SAS cells displayed a marked increase in DR5 expression (Kok et al., 2009).

Psoralidin is a coumarin with notable anticancer activity against prostate cancer LNCaP cells and cervical cancer HeLa cells. Psoralidin considerably enhanced DR5 expression in cervical cancer cells, thus improving TRAIL mediated apoptosis (Bronikowska et al., 2012). Similar results were noted in Psoralidin treated TRAIL resistant LNCaP cells as evidenced by marked increase

in percentage of the apoptotic cells (Szlizka et al., 2011).

Phenethyl isothiocyanate

It is encouraging to note that proliferation potential of CD44^{high/+}/CD24^{low/-} expressing cancer stem cells was notably reduced upon treatment with Phenethyl isothiocyanate (PEITC). PEITC exerted its effects primarily through upregulation of DR4 and DR5. Mice transplanted with PEITC pretreated CSCs did not show significant tumor development (Wang et al., 2014). PEITC notably enhanced apoptosis in TRAIL resistant glioma cells by stimulating expression of DR5 (Lee et al., 2014). Mechanistically it has been shown that PEITC induced

Table 1.

Coumarin/Coumarin Derivatives	Cells/Cell lines	Role in Apoptosis	Reference
Diversin	5637 cells	Chromatin condensation DNA damage Activation of Caspase-3	Haghighitalab et al (2014)
5,7-dihydroxy-4-methyl-6-(3-methylbutanol)-coumarin (DMAC)	Colon cancer HCT116 and LOVO	Chromatin condensation Cleavage of Caspase-3 Poly ADP-ribose polymerase (PARP) expression Loss of antiapoptotic protein (Mcl-1, Bcl-xL) JNK suppression	Lin et al (2014)
S009-131	Hela/C33A	G2/M phase arrest Upregulation of Bax/Bcl-2, ROS, PUMA and p53 Activation of Cytochrome-C, Caspase-3,7 and 9	Singh et al (2014)
(BCHHD)7C, (BCHHD)8C and (BCHHD)10C	Panc-1, Hep-G2 and CCRF	Cytotoxicity and activation of Caspase-3 and 7 G2/M phase arrest Upregulation of CDKN1A, DDIT4 and GDF-15 Downregulation of CDC2, CDC2, CDK2	Nasr et al (2014)
Coumarin analog 5a-J	Ehrlich's ascites carcinoma (EAC) Dalton lymphoma ascites (DLA)	Antiangiogenesis	Vijay et al (2014)
4-(1,2,3-triazol-1-yl) coumarin conjugate	Human breast carcinoma MCF-7 Colon carcinoma SW480 Lung carcinoma A549	G2/M phase arrest	Zhang et al (2014)
Coumarin-quinone derivative SV37	MDA-MB-231	Generation of ROS pCDK accumulation DNA damage Inhibition of CDC25 isoforms	Bana et al (2013)
Esculetin/6,7-dihydroxycoumarin	Human colon cancer	Inhibition of Wnt- β catenin pathway Disrupt the formation of β -catenin-Tef complex	Lee et al (2013)
Coumarin-3-carboxylic acid (HCCA) + Valporic acid (VAP)	Lung cancer	Upregulation of Bax Activation of Caspase-3 and PARP-1 Release of Cytochrome-C Downregulation of Bcl-2, Cyclin D1, NF-kB, AKT, EGFR, VEGFR2 and c-Met	Liu et al (2013)
Dentatin	PC-3 LNCaP prostate cancer Normal prostate epithelial cell line (RWPE-1)	Generation of ROS Downregulation of Bcl-2, Bcl-xL and Survivin NF-kB inhibition Activation of Caspase-3,7 and 9 DNA fragmentation	Arbab et al (2012)
3-(4-(dimethylamino)ethoxy)-phenyl)-7-methoxy-4-phenylcoumarin 5 3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-7-methoxy-4-phenylcoumarin 6, 3-(4-(2-(diethylamino) ethoxy)phenyl)-7-methoxy-4-methylcoumarin 7	Human lung (A549) cancer	Upregulation of Bax Downregulation of Bcl-2	Musa et al (2012)
Osthol	HCC (Heptacellular carcinoma)	Suppression of NF-kB Promoting the expression of Bcl-2 family, TRAF family, TNF ligand family, TNF receptor family, Death domain family, CIDE domain and effector domain family and CARD family	Zhang et al (2012)

apoptosis in HN22 oral cancer cells by functionalizing p38 MAPK. Inhibition of p38 MAPK in cancer cells considerably reduced PEITC induced biological effects (Huong et al., 2012). β -Phenylethyl isothiocyanate (PEITC) is a bioactive component isolated from cruciferous vegetables. PEITC treated cervical cancer cells displayed a marked decrease in phosphorylated levels of (ERK)1/2. Moreover DR4 and DR5 were remarkably enhanced after treatment of cervical cancer cells with PEITC (Huong et al., 2011).

Piperlongumine

Piperlongumine (PL), is a natural alkaloid isolated from fruit of the Long pepper and has shown potent anticancer activity. There is a recent evidence suggesting that Piperlongumine treated cancer cells had functionally inactive Akt and mTORC1 that consequently induced autophagy. However, chemical inhibition of autophagic

response induced apoptosis in Piperlongumine treated cancer cells (Makhov et al., 2014) . Piperlongumine has been shown to trigger production of Reactive Oxygen Species (ROS) in ovarian cancer cells. Combinatorial approach consisting of low dose of Piperlongumine / cisplatin or paclitaxel worked synergistically to exert biological effects (Gong et al., 2014). Piperlongumine treated prostate cancer cells displayed a marked decrease in NFkB activity and nuclear accumulation of p50 and p65 subunits was also inhibited (Ginzburg et al., 2014). JNK and p38 were noted to be active in Piperlongumine treated LN229 and U87 glioblastoma multiforme cells. Chemical inhibition of JNK and p38 drastically abrogated piperlongumine induced apoptosis (Liu et al., 2013). There is evidence of piperlongumine induced activation of ERK in HT-29 colon cancer cells. Treating HT-29 cells with MEK inhibitors partially effected piperlongumine induced apoptosis (Randhawa et al., 2013).

Table 2.

Piperlongumine (PL)	Cancer/Cancer Cells/ Cancer Cell lines	Role in apoptosis	References
Piperlongumine (PL)	Human ovarian cancer cells	G2/M phase arrest ↑ROS	Gong et al (2014)
Piper longumine combined with X-rays	Human breast cancer (MDA-MB-231) cells	↑ROS ↓Bcl-2 ↑Bax.	Yao et al (2014)
Piperlongumine (PL)	Human breast cancer cells	G1-phase arrest ↓NF-kB ↓p-Akt, ↓p70S6K1, ↓4E-BP1, ↓cyclin D1, ↓Bcl-2, ↓p53 ↑Bax ↑Cytochrome-C	Shrivastava et al (2014)
----	Breast cancer	Inhibition of Stat-3 nuclear translocation Inhibition of ligand-induced and constitutive Stat-3 phosphorylation Modulated expression of multiple Stat-3 regulated genes	Bharadwaj et al (2014)
----	Prostate, Kidney and Breast cancer	↓Akt downstream signaling ↓mTORC1 activity	Makhov et al (2014)
----	Prostate cancer cells	↓NF- κ B DNA-binding activity	Ginzburg et al (2014)
----	Glioblastoma multiforme (GBM) cells (LN229 and U87)	↓Nuclear translocation p50 and p65 subunits Attenuated expression of IL-6, IL-8, MMP-9, and ICAM-1 Activation of ROS ↑JNK ↑ p38	Liu et al (2013)
----	Mouse B-lymphoma cells	↓EBV-encoded LMP1, cellular Myc, and constitutive NF- κ B activity ↓LMP1-Myc-NF- κ B-regulated target genes including Aurka, Bcat1, Bub1b, Ccnb1, Chek1, Fancd2, Tfrc and Xrec6. Of note and p21(Cip1)-encoding Cdkn1a, independent of changes in Trp53 mRNA levels and p53 DNA-binding activity	Han et al (2013)
----	Colon cancer cells HT-29 cells	↑MEK/ERK pathway	Randhawa et al (2013)

Piperlongumine activity against breast cancer

Piperlongumine induced ROS generation in MDA-MB-231 cells has been noted to be enhanced in radiation exposed cancer cells. Bax expression was also reported to be increased in MDA-MB-231 cells (Yao et al., 2014). It has been experimentally verified that Piperlongumine interacted with conserved domain of PI3K and mTOR kinases in triple negative breast cancer cells. NF- κ B pathway was also notably repressed in treated cancer cells (Shrivastava et al., 2014). Emerging evidence also suggests that Piperlongumine treated breast cancer cells did not show nuclear accumulation of phosphorylated STATs. Moreover, ligand induced and constitutively activated STATs were also significantly inhibited in Piperlongumine treated breast cancer cells (Bharadwaj et al., 2014).

Piperlongumine treated breast cancer cells displayed an increase in C/EBP homologous protein (CHOP) expression and its target gene DR5. The results also revealed that CHOP mediated upregulation of DR5 was ROS dependent and treatment of cancer cells with ROS scavenger compromised Piperlongumine induced increase in CHOP and DR5. It was concluded that TRAIL induced apoptosis was potentiated by treating cancer cells with Piperlongumine (Jin et al., 2014).

Luteolin

Luteolin has been shown to be effective against human papillomavirus (HPV) infected cervical cancer cells. The results revealed that luteolin considerably reduced HPV encoded proteins including E6 and E7. Moreover, it is worth mentioning that there was considerable increase in DR5 and FADD in luteolin treated cervical cancer cells. Intrinsic pathway was activated via activation of caspase-3 by caspase-8. Moreover, efflux of cytochrome c from mitochondria was also noted along with inhibition of Bcl-2 and Bcl-xL (Ham et al., 2014). Luteolin treated 786-O renal cell carcinoma cells displayed a decrease in Mcl-1 and FLIP levels. Moreover, Akt and STAT were also noted to be biologically inactive in Luteolin treated cancer cells (Ou et al., 2014). Luteolin and TRAIL worked with effective synergy and considerably inhibited tumor growth in mice xenografted with A549 lung cancer cells (Yan et al., 2012).

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