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REVIEW

# Restoring TRAIL Mediated Signaling in Ovarian Cancer Cells

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**Abstract** Ovarian cancer has emerged as a multifaceted and genomically complex disease. Genetic/epigenetic mutations, suppression of tumor suppressors, overexpression of oncogenes, rewiring of intracellular signaling cascades and loss of apoptosis are some of the deeply studied mechanisms. In vitro and in vivo studies have highlighted different molecular mechanisms that regulate tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) mediated apoptosis in ovarian cancer. In this review, we bring to limelight, expansion in understanding systematical characterization of ovarian cancer cells has led to the rapid development of new drugs and treatments to target negative regulators of TRAIL mediated signaling pathway. Wide ranging synthetic and natural agents have been shown to stimulate mRNA and protein expression of death receptors. This review is compartmentalized into programmed cell death protein 4, platelet-derived growth factor signaling and miRNA control of TRAIL mediated signaling to ovarian cancer. Mapatumumab and PRO95780 have been tested for efficacy against ovarian cancer. Use of high-throughput screening assays will aid in dissecting the heterogeneity of this disease and increasing a long-term survival which might be achieved by translating rapidly accumulating information obtained from molecular and cellular studies to clinic researches.

**Keywords** TRAIL · Ovarian cancer · Apoptosis

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## Introduction

Ovarian cancer is a complicated disease. A lot of epidemiological and clinical evidence suggest that specific genetic, epigenetic and environmental factors are highly associated with ovarian cancer development (Chang et al. 2002a, b; Salani et al. 2007). There are different classification systems for ovarian cancer, including high-grade serous, endometrioid, clear cell, mucinous, and low-grade serous (Prat 2012) (Table 1).

Cutting-edge experimental methodologies have started to de-complex the proteome into subcategories of pro-apoptotic and anti-apoptotic proteins. Massive information related to tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) mediated signaling reveals the near-complete definition of cancer subproteomes, which identifies the alterations in signaling pathway. We summarize recent achievements in basic and translational

**Table 1** Ovarian cancer types

| | | |
|---|---|---|
| Type I | Low-grade serous, low-grade endometrioid, clear cell, and mucinous carcinomas | Kurman and Shih Ie (2011) |
| Type II | High-grade serous, high-grade endometrioid, and undifferentiated carcinomas | Kurman and Shih Ie (2011) |

researches. At the cellular level, a considerable progress has been made in understanding the key biochemical steps during apoptosis and it has been persuasively revealed that binding of a trimeric ligand such as TNF, TRAIL, or Fas ligand may trigger recruitment of adaptor proteins (FADD) to the death domains (DD) of the receptor. Expression analysis of TRAIL has revealed divergent data. For example, higher expression of TRAIL in tumor cells was noted to be associated with a favorable outcome in a cohort of 120 patients (Lancaster et al. 2003). In contrast, another report did not find any possible association between TRAIL expression and favorable outcome in a smaller cohort of 68 patients. However, stromal expression of TRAIL may act as a strong indicator of overall survival. For example, TRAIL receptors 1 (DR4) and 2 (DR5) were downregulated and cellular caspase-8 (FLICE)-like inhibitory protein (cFLIP) was overexpressed in ovarian tumors (Horak et al. 2005a). Lower DR5 expression was noted in ovarian serous cystadenoma and primary epithelial ovarian carcinoma (EOC) as compared to metastatic EOC samples (Braga Lda et al. 2014). Epigenetic silencing of DR4 was reported in 8–27 % of ovarian cancer samples (Horak et al. 2005b) but other report found that DR4 was found to be highly expressed in ovarian cancer cells (Dong et al. 2008).

The intracellular signals communicated upon interaction of TRAIL with Death Receptor (DR) are shown in Fig. 1. In detail, DR, FADD and procaspase-8 together form Death Inducing Signaling Complex (DISC). Two recent reports suggest that T3SS effector NleB-like protein (NleB1), a protein belonging to *Escherichia coli* type III secretion system, is involved in impairing TRAIL mediated signaling via inhibition of DISC complex formation. It is surprising that NleB1 can regulate TRAIL mediated signaling via post-translational modification of Arg 117 in DD domain of FADD. The function of cellular *N*-acetylglucosamine transferase activity of NleB1 is to inhibit of DISC formation and consequently activate caspase-8 (Li et al. 2013a; Pearson et al. 2013). However, cFLIP containing two death effector domains is a negative regulator of TRAIL mediated apoptosis through its competitive inhibition of conversion of procaspase-8 into caspase-8. Detailed structural studies provide wealth of information about different caspases. It is known that caspase-8, a dominant death receptor-activated caspase, can be recruited by the TRAIL receptors (DR4 and DR5). Intrinsic pathway operates through mitochondria after processing Bid via caspase-8. Truncated Bid moves into mitochondria and there is an outer membrane permeabilization. Subsequently, mitochondria may release different pro-apoptotic proteins, including cytochrome c, apoptosis-inducing factor, endonuclease G, Smac/DIABLO and Omi/HtrA2 (not shown).

Smac mimetics and cells reconstituted with Smac have shown a great potential in restoring TRAIL mediated apoptosis. BID, BAD, BIM, NOXA, and PUMA are the members of a mammalian BH3-only protein family and are involved in the induction of apoptosis. BCL-2, BCL-XL, MCL1, and BCL-W are structurally characterized on the basis of four BCL-2 homology (BH) domains. Mechanistically, BH3-only protein can regulate oligomerization of apoptosis inducing BCL-2-family members such as BAX and BAK. However, anti-apoptotic BCL-2 proteins negatively modulate BH3-only protein mediated oligomerization of BAX and BAK.

In this section, we have attempted to provide an overview of the proteins downstream to DISC. However, there is increasing evidence that indicates the formation of secondary signaling complex in TRAIL treated cancer cells. This signaling complex further activates downstream effectors including NF-κB, p38, c-Jun N-terminal kinases (JNK) and extracellular signal-regulated kinases (ERK). In the next section, we discuss segmented view of divergent roles of these effectors in regulation of ovarian cancer cells.

## Secondary Signaling Complex

### NF-κB

In thyroid carcinoma cells, TRAIL treatment may induce activation of NF-κB by IκB kinase (IKK). R-Roscovitine, a cyclin-dependent kinase inhibitor, can effectively inhibit the IKK/NF-κB signaling axis. Intriguingly, cells reconstructed with IKKβ can display the impairment of TRAIL mediated apoptosis in cancer cells (Festa et al. 2009). Consistently, lung cancer cells infected with adenovirus vectors encoding TRAIL and IKKβKA mutant result in an enhanced apoptosis in TRAIL resistant cancer cells (Aydin et al. 2010). Furthermore, the miRNA expression is also controlled by TRAIL mediated signaling. Furthermore, in TRAIL treated cancer cells miR-146a may be triggered by NF-κB. miR-146a can negatively regulate CXCR4 thus inhibiting migratory potential of cancer cells (Wang et al. 2013a). NF-κB and JAK/STAT signaling pathway are essential for the survival of ovarian cancer cells. Experiments of butenal-treated ovarian cancer cells revealed that phosphorylated STAT protein levels were considerably reduced. Moreover, butenal exerted its pro-apoptotic

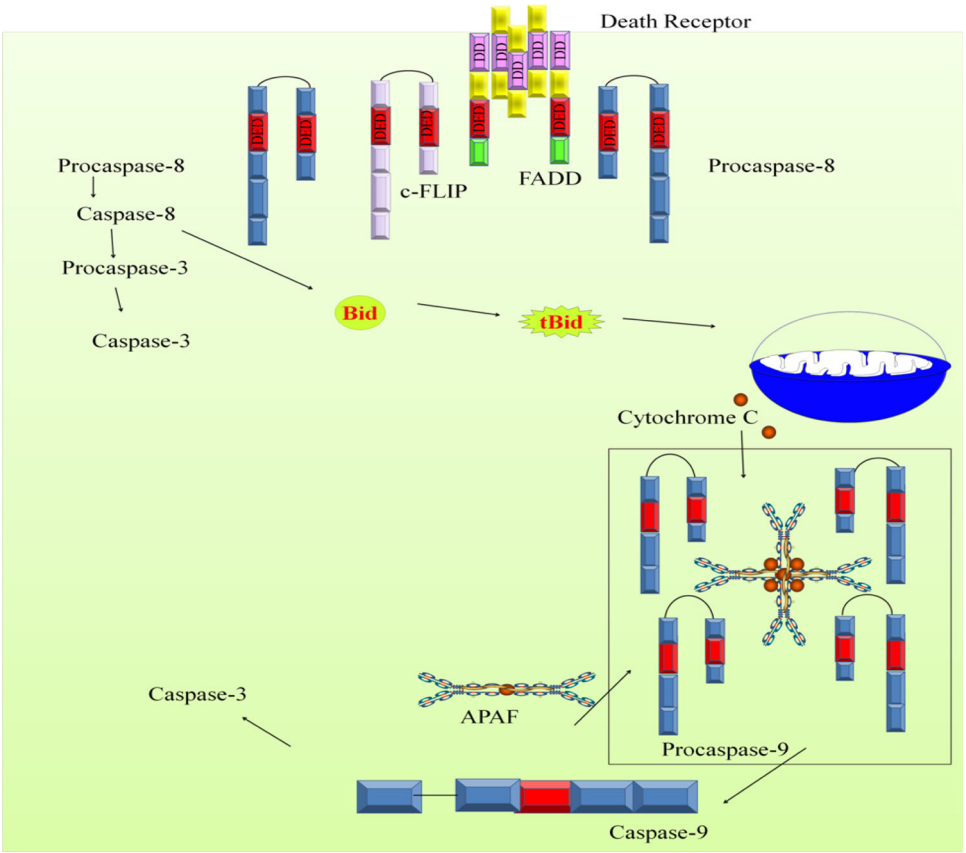


**Fig. 1** Intracellular signals communicated upon interaction of TRAIL with Death Receptor (DR). Categorically, TRAIL mediated signaling is subdivided into intrinsic and extrinsic pathways. Extrinsic pathway operates through DR mediated transduction of signals that result in formation of Death Inducing Signaling Complex (DISC). DISC is composed of DR, FADD and procaspase-8. Later, activated caspase-8 can activate downstream caspase-3. Intrinsic pathway is triggered upon truncation of Bid. Truncated Bid moves into the mitochondria that makes the membrane permeable to release of cytochrome c, SMAC/DIABLO (not shown). Cytochrome c, pro-caspase-9 and apoptotic protease-activating factor (APAF) together form the apoptosome. Activated caspase-9 in turn activates caspase-3

effects via activation of both extrinsic and intrinsic pathways (Cho et al. 2014). Although recent evidence is highlighting how TRAIL induced pro-survival signaling, NF-κB mediated control of miRNA has added another layer of investigation that needs to be studied in detail.

## JNK

Preclinical studies and functional genomics provide convincing evidence that JNK is involved in transcriptional upregulation of DR in cancer cells. Increasingly it is being noted that reactive oxygen species generation triggered specific signaling axis stimulated the expression of DRs that included JNK and CAAT/enhancer-binding protein homologous protein (CHOP). In colorectal and breast cancer cells, JNK/CHOP/DR5 signaling axis was reported to contribute to transcriptional control of DR5 (Gopalan et al. 2013; Sung et al. 2012). Activation of JNK is also triggered by the death-domain kinase RIP. In vitro studies have shown that RIP and TNF receptor-associated factor 2 (TRAF2) are essential for TNF-induced activation of NF-κB and JNK. Ectopic expression of Myc-RIP or Flag-TRAF2 with HA-JNK1 in $RIP^{-/-}$ or $TRAF2^{-/-}$ cells, notably restored JNK activation in response to TRAIL. Transient transfection of the dominant negative mutant RIP in TRAIL treated cells did not activate JNK (Lin et al. 2000).

## ERK-Mediated Regulation of TRAIL Signaling

Mitogen-activated protein kinases (MAPKs)/extracellular signal-regulated kinase kinase kinases (MEKKs) are activated in growth factor treated cells. MEKKs are upstream modulators of the three-module cascade of MAPKs. JNK, p38 and ERK are MAPKs and located downstream in signaling module. The pERK 1/2 can inhibit pro-caspase-8 by phosphorylating at its S387 in TRAIL treated ovarian cancer cells. Ovarian cancer cells expressing non-phosphorylatable counterpart (S387A) of pro-caspase-8 demonstrated a higher apoptotic rate upon TRAIL treatment (Mandal et al. 2014).

ERK is an important regulator of growth factor mediated signaling to regulate pro-apoptotic and anti-apoptotic proteins. In ovarian cancer cells, thioredoxin reductase inhibitor (TRI) treatment may enhance sensitivity to TRAIL. It was explored that ASK1, also known as MAP3K5, positively regulated ERK in TRAIL resistant ovarian cancer cells. Gene silencing strategies to targeted inhibition of ASK1 may impair ERK kinase activity and consequently inactivate its downstream substrates. Similarly, TRI treatment of ovarian cancer cells was reported to be involved in the signaling axis via ASK/ERK/SP1. Therefore, it seems clear that SP1 transcriptionally regulates death receptor and inactivates SP1 to repress the

expression of its target genes (Lin et al. 2013). Yet another anti-apoptotic protein Mcl-1 was found to be upregulated via ERK1/2 and Elk-1 signaling axis (Goncharenko-Khaider et al. 2012). These seemingly opposing paradigms need detailed research related to TRAIL induced signaling in ovarian cancer cells. ERK and JNK have a divergent role in suppression and promotion of ovarian cancer.

## Darker Side of the TRAIL

However, it is worth mentioning that despite tremendous breakthroughs made in molecular oncology which have helped in improving our understanding of TRAIL mediated apoptosis in cancer cells, certain clues highlight the role of TRAIL in promoting cancer. Transplantation of pancreatic ductal adenocarcinoma cells in the severe combined immunodeficiency (SCID) mice resulted in considerably enhanced metastatic spread. Moreover, there was a notable rise in the number of liver metastases promoted by TRAIL (Trauzold et al. 2006). Mechanistically, TRAIL treated mutant PIK3CA-expressing colorectal cancer cells had caspase-8 mediated cleavage of rho-associated, coiled-coil containing protein kinase (ROCK)-1 (Ehrenschwender et al. 2010). It was verified that targeted inhibition of ROCK-1 in the fraction of PIK3CA-mut cells with rounded shape resulted in notable change in cellular morphology. Surprisingly, an enforced expression of cFLIPs in mutant PIK3CA-expressing cells inhibited amoeboid cellular morphology (Ehrenschwender et al. 2010). Cholangiocarcinoma cells treated with TRAIL may display a migratory and invasive potential (Ishimura et al. 2006). Likewise, SMAC mimetic was effective in reducing extrahepatic metastases. Additionally, TRAIL treated cells were reported to have the functionally active NF-κB to consequently triggered the expression of target genes including matrix metalloproteinase (MMP)-7. Astonishingly, SMAC mimetic-treated cholangiocarcinoma cells had remarkably reduced MMP-7 because of inhibition of NF-κB (Fingas et al. 2010). Thyroid hormone treated thyroid hormone receptor (TR)-overexpressing hepatoma cells were reported to display transcriptional upregulation of TRAIL as well as MMP-2, MMP-7, MMP-9 and Bcl-XL (Chi et al. 2012). In TR-overexpressing cells xenografted SCID mice, tumor size and the metastatic index were significantly greater in hyperthyroid mice as compared to normal thyroid or hypothyroid animals. Chronically exposed human ovarian cancer OVCAR3 cells to increasing concentrations (10–350 ng/mL) of TRAIL resulted in the generation of the TRAIL resistant subpopulation but its DR4 and DR5 levels were unchanged. Effector caspase-3 may alter in TRAIL resistant sub-population and proteasome-mediated degradation of caspase-3 was noted. Gene silencing against X-linked inhibitor of apoptosis protein (XIAP) can increase activated caspase-3 (Lane et al. 2006).

Moreover, ovarian cancer cells may overexpress the antiapoptotic protein family member that results in the defective apoptotic signaling. In the upcoming sections, we briefly provide an overview of pro-apoptotic and anti-apoptotic proteins. Different approaches to target anti-apoptotic proteins, or agents can either promote the extrinsic and intrinsic pathway or stimulate the expression of DRs. Later, we systematically provide an overview of role of programmed cell death protein 4 (PDCD4), platelet-derived growth factor (PDGF) signaling and miRNAs in regulation of TRAIL mediated signaling. We also provide some relevant information from other cell type specific studies uncovering signaling circuitry for a better understanding of TRAIL mediated signaling.

## FLIPs and Caspases: Imbalance of Anti-Apoptotic and Pro-Apoptotic Proteins

Various proteins are overexpressed in ovarian cancer cells and severely impair the efficacy of TRAIL. As indicated in previous section, cFLIP has emerged as an important negative regulator in abrogating apoptosis in different cancer types in TRAIL treated cells. Recently, upregulated expression of FLIP in 30 % of the granulosa cell tumor of the ovary and expression of Bcl-2 was found to be over-expressed in 75 % samples (Yoo et al. 2012). Xenografting c-FLIP silenced A2780 ovarian tumor cells in female nude/nude mice may inhibit tumor growth of xenografts in nude mice (El-Gazzar et al. 2010).

Activation of caspase-3 by caspase-8 and caspase-9 is essential for an effective TRAIL mediated signaling. cFLIP may compete with caspase-8 in communicating the signals to its downstream effectors. Different compounds including salinomycin, Smac mimetics, G-rich T-oligos, mifepristone and histone deacetylase inhibitor (HDACi) have been used to test the efficacy in targeting cFLIP or activating caspase pathway in TRAIL treated cells. In the next paragraph, we discuss how these compounds can display the effective targeting of FLIP (Table 2).

A shown in Table 2, T-oligos are DNA oligonucleotides homologous to the telomere 3′ overhang region and G-rich T-oligos is an advanced form of T-oligos. G-rich T-oligos (GT-oligos; oligonucleotides with homology to telomeres) were reported to reverse TRAIL resistant phenotype to TRAIL sensitive. FLIPs were suppressed and JNK was activated in GT-oligos treated ovarian cancer cells. Additionally, capase-8 and caspases 3/7 were also activated (Sarkar and Faller 2013). FLIPs were also suppressed in salinomycin-treated cisplatin-resistant ovarian cancer cells (Parajuli et al. 2013). LBW242, a mimic of SMAC/

**Table 2** List of synthetic and natural compounds tested for efficacy to target protein network of apoptosis

| | DR4 | DR5 | Caspase | FLIP | Bax/Bak | Bcl-2 |
|---|---|---|---|---|---|---|
| G rich T oligos | | | ↑ | ↓ | | |
| Salinomycin | | ↑ | ↑ | ↓ | | |
| Pomolic Acid | | ↑ | | | | |
| Mifepristone | | ↑ | | ↓ | | |
| Methylenedioxy quinolin | | ↑ | | | | |
| Radicicol | | | ↑ | | | |
| Diarylheptanoid | | | | | | |
| Celastrol | ↑ | ↑ | | | | |
| AspidinBB | | | | | ↑ | ↓ |

DIABLO, may induce apoptosis in ovarian cancer cells, however, overexpressing FLIP in cancer cells can abolish LBW242 induced apoptosis. RNA interference strategies further confirmed that targeting of FLIP in ovarian cancer cells considerably enhanced apoptosis in LBW242 treated cells (Petrucci et al. 2012). Mifepristone repressed antiapoptotic proteins including FLIP and Bcl-1 (Min et al. 2012). Combined treatment of progesterone and medroxyprogesterone acetate displayed a potential in effectively targeting FLIP and concomitant induction of TRAIL mediated apoptosis (Syed et al. 2007).

Growth factor mediated signaling is contributory to resistance against TRAIL. Different studies have shown that EGFR/PI3K/AKT signaling axis is involved in a transcriptional upregulation of oncogenes. Trichostatin A (TSA), a HDACi, also repressed the expression of FLIP by inhibition of EGFR/PI3K/AKT mediated cellular signaling (Fig. 2a). Mitochondrial pathway was activated in TSA treated cancer cells (Park et al. 2009). Astonishingly, there are additional target genes which are triggered by PI3K/AKT and SAPK/JNK pathways (Fig. 2b). For example, an anti-apoptotic protein survivin may be regulated by these pathways. Moreover, these pathways are activated in follicle stimulating hormone treated ovarian cancer cells (Huang et al. 2011). Surprisingly, cisplatin-resistant ovarian cancer cells upon curcumin treatment may activate both caspase-8 and caspase-9 mediated pathways (Wahl et al. 2007).

## Approaches to Stimulate the Expression of DR4 and DR5

Resistance against TRAIL in cancer cells has been extensively studied. Regarding the underlying mechanisms, starting from over-expression of anti-apoptotic proteins to loss of pro-apoptotic proteins may improve our understanding. Moreover, notable downregulation of DR4 and DR5 was frequently observed in different cancer types. In this section, we briefly describe various approaches to stimulate the expression of DR4 and DR5 in ovarian cancer cells. Moreover, we also discuss divergent data to death receptor regulation by p38 MAPK in ovarian cancer cells.

A shown in Table 2, salinomycin-treated cisplatin-resistant ovarian cancer cells displayed drastically increased activity of caspases 3/8 and upregulated DR5 (Parajuli et al. 2013). Pomolic acid, a *Cecropia pachystachya*-derived pentacyclic triterpene, is involved in a transcriptional upregulation of DR5 along with concomitant activation of caspase-8, -9 and -3 (Yoo et al. 2013).

In Fig. 3, some agents that modulate the TRAIL mediated signaling in ovarian cancer were provided. For example, mifepristone was also reported to upregulate DR5 (Min et al. 2012). Astonishingly, there is a contradictory data related to p38 MAPK mediated upregulation of death receptors. Data indicate that expression of DRs is in p38 MAPK dependent and independent manner. Exposure of ovarian cancer cells to series of methylenedioxyquinolin-4-one derivatives resulted in p38 mediated upregulation of DR5 (Lee et al. 2011b). Surprisingly, treating ovarian cancer cells with celastrol may activate p38 MAPK. To confirm whether p38 MAPK is directly involved in stimulating the expression of DR4, MAPK inhibitor was used but the expression of DR4 was not changed. Moreover, celastrol increased the expression of DR4 and DR5 (Zhu et al. 2010).

## Regulation of Bax, Bid, Bcl-2 and Bcl-xL by Different Compounds

TRAIL induced a decrease in Bid, Bcl-2, Bcl-xL, and survivin protein levels but an increase in Bax levels (Kim et al. 2012). Several compounds that may target protein network of apoptosis were discussed (Table 2 and Fig. 3). For example, radicicol enhanced TRAIL-induced cell death (Kim et al. 2012). Diarylheptanoids such as hirsutenone and oregonin may activate caspase-8- and Bid-dependent pathways in ovarian cancer cells (Lee et al. 2012). Aspidin BB, an effective phloroglucinol derivative from *Dryopteris fragrans* (L.) Schott, is reported to repress the expression of Bcl-2 and a simultaneous stimulation of the expression of Bax (Sun et al. 2013b).

## Strategies to Restore Apoptosis in Ovarian Cancer Cells

Resistance to TRAIL mediated signaling has emerged as a major stumbling block as confirmed by preclinical studies. Synthetic and natural compounds have promising results in

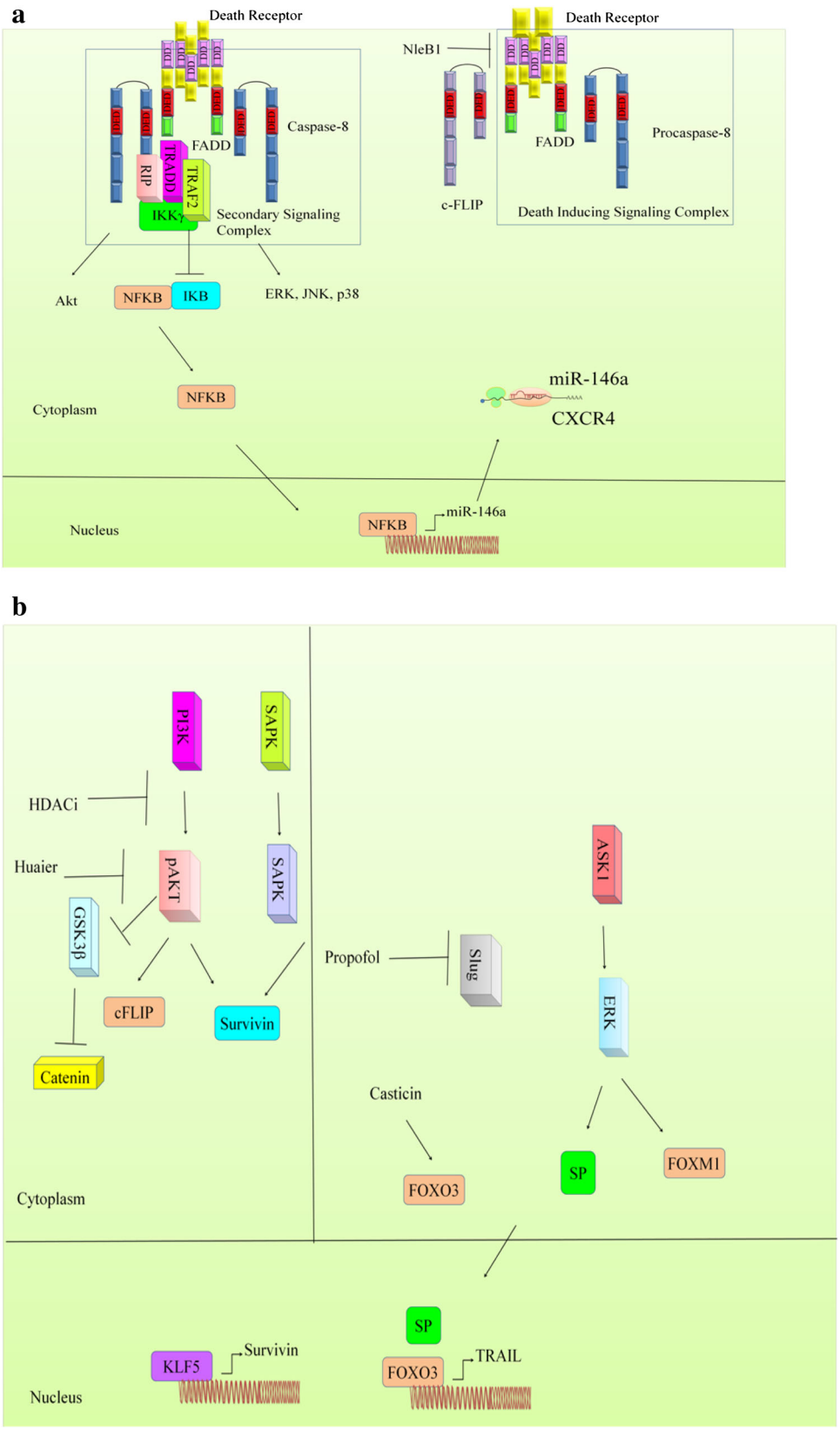


**Fig. 2** **a** Two types of signaling axis in cancer cells treated with TRAIL. There is a regular formation of Death Inducing Signaling Complex (DISC) in cancer cells treated with TRAIL. However, in many situations, there is a secondary complex formation downstream to DISC that is composed of TRADD, TRAF2, RIP, IKKγ. The secondary complex is involved in activation of Mitogen Activated Protein Kinases (MAPKs) including p38, JNK and ERK. In addition, Akt and NF-κB are also activated in TRAIL treated cancer cells. NF-κB has been shown to trigger the expression of miR-146a in cancer cells. miR-146a negatively regulates CXCR4 in cancer cells thus repressing migratory potential of cancer cells. It has also been shown that microbial protein NleB1 also controls TRAIL mediated apoptosis via inhibition of FADD. Inhibition of FADD restricts formation of DISC. **b** PI3K/Akt signaling axis is involved in inhibiting GSK3β mediated inhibitory effect on catenin via inactivation of GSK3β by pAkt. Huaier inhibited Akt mediated inhibitory effect on GSK3β. Slug is a transcription factor that is upregulated in paclitaxel-treated ovarian cancer cells and a target for propofol. ASK1/ERK regulates activation of SP and FOXM1. SP and FOXO3 upregulate the expression of TRAIL. SAPK and pAkt modulate survivin and cFLIP in cancer cells. KLF5 transcriptionally upregulates the expression of survivin. ⊥ indicates inhibitory action. *Different colours* of SAPK indicate inactive and active forms. *Lemon Green* indicates SAPK inactive form. *Purple* indicates SAPK active form

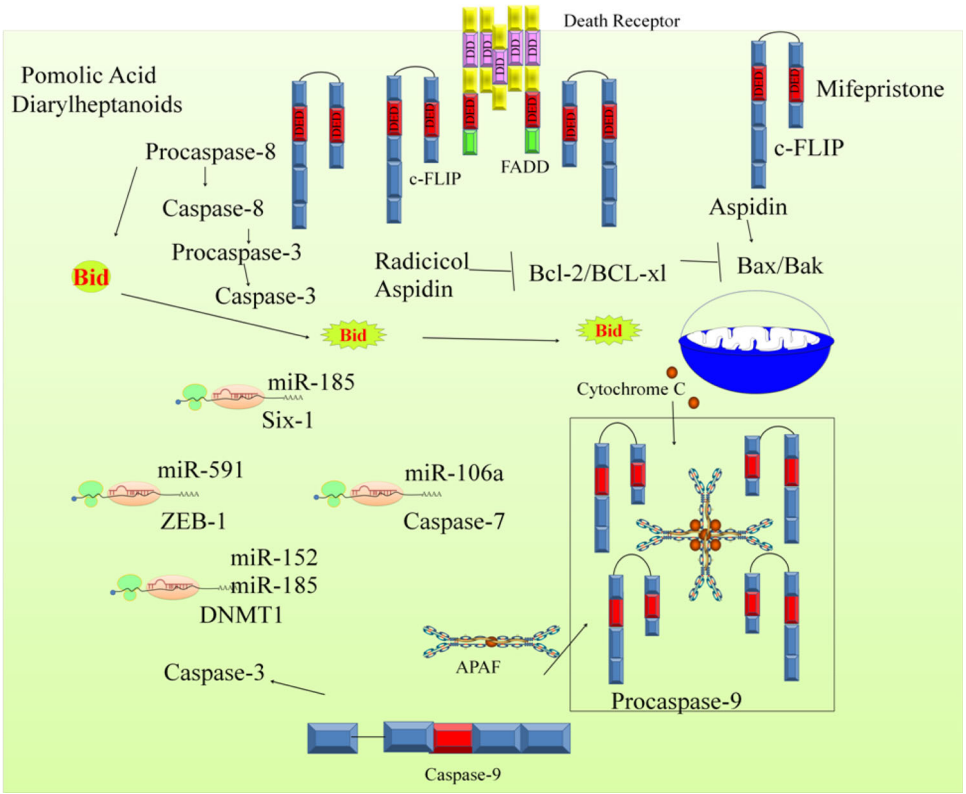


**Fig. 3** TRAIL mediated signaling ovarian cancer highlighting extrinsic and intrinsic pathways to trigger apoptosis in ovarian cancer cells. Moreover, miRNA regulation of pro-apoptotic and anti-apoptotic proteins is also shown

preclinical studies for exploring the extrinsic and intrinsic pathways, regulation of death receptors, and control of pro-apoptotic and anti-apoptotic proteins. Guanylate cyclase activator YC-1 treatment was found to resensitize resistant ovarian cancer cells to TRAIL (Lee et al. 2011a).

IVHD-valtrate, one of the most active *Valeriana jatamansi* derivatives, has been shown to inhibit the expression of Mdm2, E2F1, Cyclin B1, Cdc25C and Cdc2 in ovarian cancer cells. Moreover, p53, p21 and p27 were reported to upregulate in ovarian cancer cells (Li et al. 2013b). In glioma cells, transient co-transfections of Cdc2 and cyclin B may substantially impair TRAIL mediated apoptosis. Cells reconstituted with Cdc2 and cyclin B were analyzed and levels of survivin and XIAP were considerably increased (Kim et al. 2005). Similar mechanism upon treatment of malignant glioma cells with capsaicin (bio-active ingredient of red chili) was reported. The results indicated that capsaicin was effective in repressing Cdc2 and cyclin b (Kim et al. 2010). As discussed previously Cdc25c, Cdc2 and cyclin B are activated in ovarian cancer cells. Therefore, targeted inhibition of these proteins will be helpful in restoring TRAIL mediated apoptosis in resistant cancer cells.

A polymethoxyflavone, namely Casticin, can be isolated from *Vitex rotundifolia* and *Croton betulaster*. Ovarian cancer cells treated with Casticin may induce apoptosis by targeting of FOXM1 and its target genes including survivin and polo-like kinase 1. ERK can act to the upstream of FOXM1 and trigger transportation of FOXM1 into the nucleus, which is essential for transcriptional upregulation of target genes (shown in Fig. 2b). FOXM1 is also a target of genistein, which is a trihydroxylisoflavone isolated from soybean, as evidenced by an enhanced apoptosis in ovarian cancer cells (Ning et al. 2012).

Moreover, Casticin-treated ovarian cancer cells displayed an activated FOXO3a. Inhibition of FOXO3a severely abrogated casticin-induced apoptosis in ovarian cancer cells (Jiang et al. 2013). FOXO3 is involved in stimulating pro-apoptotic genes in different cancer cells. In lymphoblastic leukemia cells, FOXO3 overexpression resulted in the restoration of sensitivity to chemotherapeutic drugs. RNA analysis revealed transcriptional upregulation of TRAIL up to 50-fold after 6 h in FOXO3 activated cancer cells (Ausserlechner et al. 2013). Concordant with the concept that FOXO3 is involved in controlling the expression of various target genes, there are some repressors which antagonize FOXO3 mediated transcriptional regulation of various genes. Recently, constitutive activation of NFIL3 nuclear factor interleukin 3 regulated (NFIL3) in cancer cells was reported to substantially impair FOXO3 mediated regulation of TRAIL gene. NFIL3 limits access of FOXO3 to the promoter of TRAIL gene in a stepwise manner by promoting the recruitment of histone deacetylase-2 (HDAC2). HDAC2 mediated deacetylation may severely abrogate acetylation of histone and repress the expression of TRAIL gene (Keniry et al. 2013).

Aqueous extract of *Trametes robiniophila murr* (Huaier) is suggested to inhibit translocation of β-catenin into the nucleus. The pathway is triggered by upstream modulators such as Akt and glycogen synthase kinase 3β (GSK3β). Wnt signaling is negatively regulated by GSK3β. Phosphorylation on Serine 9 has an inhibitory effect on activity of GSK3β. Different kinase such as Akt is involved in inhibiting the activity of GSK3β via phosphorylation of Serine 9. Aqueous extract treated ovarian cancer cells may remarkably reduce phosphorylated-AKT levels. Loss of activation of AKT can rescue the GSK3β activity (Fig. 2b). Altogether there was notable decrease in the cytoplasmic protein level of GSK3β and marked decrease in its nuclear localization (Yan et al. 2013).

## Restoring Apoptosis in Drug-Resistant Ovarian Cancer Cells

Overexpression of P-glycoprotein in taxane-resistant ovarian cancer cells may lead to loss of apoptosis in paclitaxel-treated cells. In contrast, selective cyclooxygenase inhibitors have shown potential in restoring apoptosis in paclitaxel-treated cells via suppression of P-glycoprotein (Lee et al. 2013). Kruppel-like factor 5 (KLF5) is overexpressed in ovarian cancer cells and stimulates the expression of survivin (Fig. 2b). Overexpression of KLF5 and its target gene survivin may induce cisplatin or paclitaxel resistance (Dong et al. 2013). Slug, a transcription factor, is upregulated in paclitaxel-treated ovarian cancer cells. HDAC inhibitor MS-275 may negatively regulate Slug protein levels and restore epithelial phenotype in nude mice xenografted with invasive MDA-MB-468 breast cancer cells resistant to TRAIL (Srivastava et al. 2010).

Slug is targeted by different synthetic compounds including propofol. Ovarian cancer cells treated with Propofol (an intravenous anaesthetic agent) displayed a decrease in Slug level (Wang et al. 2013b). Piceatannol is a hydroxylated analogue of resveratrol. Grapes, passion fruit, white tea, and Japanese knotweed are the rich sources of Piceatannol. Piceatannol can enhance cisplatin sensitivity and induce apoptosis. It operates through p53 mediated upregulation of pro-apoptotic protein NOXA and concomitant activation of caspase-3 (Farrand et al. 2013). On a similar note, targeted inhibition of STAT3 by decoy oligodeoxynucleotides considerably reduced MMP-2, MMP-9 and Bcl-2 in ovarian cancer cells (Zhang et al. 2013).

Bioactive ingredients including ginkgolide and quercetin, isolated from *Ginkgo biloba*, are effective against ovarian cancer (Ye et al. 2007). Quercetin can overcome resistance against TRAIL in cancer cells and transcriptionally upregulate protein stability of DR5 (Jung et al. 2010). Concordantly, DR5 may be triggered via SP1. Moreover, quercetin can trigger proteasome-mediated c-FLIP degradation (Kim et al. 2008). It was reported that pretreatment with phytochemicals to platinum drug is efficacious in overcoming resistance in cancer cells (Nessa et al. 2011). Multitargeting of cancer proteome by quercetin attracted scientists to further improve its delivery to the target sites. In accordance with this notion, quercetin is functionalized with nanoparticles. Quercetin may be encapsulated into monomethoxy poly(ethylene glycol)-poly(ε-caprolactone) (MPEG-PCL) micelles. Nanofunctionalized quercetin may induce regression of xenografted ovarian tumor cells (Gao et al. 2012). PEGylated liposomal quercetin can restore apoptosis in cisplatin-resistant cancer cells (Long et al. 2013).

## miRNA Interferes with TRAIL Mediated Signaling

TRAIL mediated signaling in ovarian cancer cells is considerably explored with emphasis on increasing list of pro-apoptotic and antiapoptotic proteins. There are also tremendous advancements in identification of effects of chemotherapeutic drugs, herbal extracts on protein network involved in TRAIL mediated signaling. However, how miRNA controls TRAIL mediated signaling in ovarian cancer cells is insufficiently studied and it needs an in-depth analysis. There are very few reports which directly provide an overview of miRNA control of TRAIL mediated signaling. We attempt to integrate fragmented updates on recently emerging information on miRNA regulation of apoptosis in ovarian cancer cells (Fig. 3).

As shown in Fig. 3, Six-1 is a homeobox protein that is frequently overexpressed in ovarian cancer cells. TRAIL mediated signaling may be impaired in Six-1 overexpressing ovarian cancer cells. Six-1 may be controlled by miRNA. Astonishingly, stable transfection of miR-185 in ovarian cancer cells notably enhanced TRAIL mediated apoptosis in ovarian cancer cells via negative regulation of Six-1 (Imam et al. 2010). When miR-106a and miR-591 are misrepresented in ovarian cancer cells and re-expression of miR-591, apoptosis is inducible. Moreover, miR-591 can negatively regulate ZEB1. Antagomirs are chemically engineered oligonucleotides which can direct against endogenous miRNA. Use of antagomirs against miR-106a was an effective strategy for inducting apoptosis as miR-106a was a negative regulator of BCL10 and caspase-7 (Huh et al. 2013). Enforced expression of miR-193a and miR-193b in ovarian cancer cells can activate caspase 3/7 and induce apoptosis (Nakano et al. 2013). MiR-152 and miR-185 are underexpressed in ovarian cancer cells and reconstitution of these miRNAs restored cisplatin sensitivity via negative regulation of DNA methyltransferase 1 (DNMT1) (Xiang et al. 2014). The relationship between

TRAIL mediated apoptosis and DNMT1 and DNMT3b has been explored in human hepatoma cells. Gene silencing of DNMT1 and DNMT3b can restore TRAIL sensitivity in resistant cancer cells primarily by upregulation of death receptors (Kurita et al. 2010). miRNA-200c is reported to underexpress in $CD117^{+}CD44^{+}$ ovarian cancer stem cells (CSCs). For a detailed analysis, $CD117^{+}CD44^{+}$ CSCs reconstituted with miR-200c were isolated from SKOV3 ovarian cancer cell line. miR-200c also is able to control ZEB-1 and Vimentin expression thus repressing epithelial to mesenchymal transition. Animal model study additionally confirmed that enforced expression of miR-200c substantially inhibited $CD117^{+}CD44^{+}$ CSCs xenograft growth and lung metastasis in vivo in nude mice (Chen et al. 2013a). miR-103 and miR-107 can restore sensitivity of resistant ovarian cancer cells to chemotherapeutic drugs via targeting of RAD51 and RAD51D (Huang et al. 2013).

Enhancer of zeste 2 (EZH2) was reported to promote cellular proliferation and enhance invasive potential of epithelial ovarian cancer cells (Li et al. 2010). It is also intriguing to note that gene silencing of EZH2 restored the expression of Dicer (an enzyme that processes miRNA) in cancer cells (Kuang et al. 2013). Enforced expression of let-7e in epithelial ovarian cancer cells considerably reduced expression of EZH2 and cyclin D1 (CCND1), thus re-sensitizing cells to cisplatin (Cai et al. 2013).

miR-222 negatively regulated P27Kip1 thus promoting cellular proliferation (Sun et al. 2013a). DGCR8 is also a regulator of miRNA biogenesis and is constitutively overexpressed in ovarian cancer cells. In vitro studies revealed that silencing of DGCR8 in cancer cells simultaneously inhibited ERK1/2 and PI3K/Akt signaling axis (Guo et al. 2013). Drug resistance can also reduce substantially via miR-199a mediated negative regulation of mTOR (Wang et al. 2013d).

## miRNA Regulation of PDCD4 in Ovarian Cancer

PDCD4, a tumor suppressor, frequently repressed in ovarian cancer. Cisplatin-resistant SKOV3 cells treated with berberine may downregulate miR-21 that rescued the expression of PDCD4 (Liu et al. 2013). In line with this concept, another contemporary study suggests regulation of PDCD4 by miR-182 (Wang et al. 2013c). Moreover, ovarian cancer cells reconstituted with PDCD4 were sensitive to cisplatin with a prominent cisplatin-induced cleavage of caspase-3 and caspase-8. Pharmacological inhibition of caspase-8 dramatically reduced cisplatin induced apoptosis in PDCD4 over-expressing ovarian cancer cells (Zhang et al. 2010). Astonishingly, there is no direct evidence highlighting relationship of TRAIL and PDCD4 in ovarian cancer cells. However, in gastric cancer cells with transient transfection of PDCD4 may restore TRAIL mediated apoptosis (Wang et al. 2010a). Intriguingly, PI3K inhibitor LY294002 treated cells may inactive Akt and activate PDCD4 to enhance TRAIL sensitivity in TRAIL-resistant gastric cancer cells (Wang et al. 2010b).

## Crystallin and TRAIL

In transient transfection of a small heat shock protein crystallin αB in ovarian cancer cells, TRAIL mediated apoptosis was abrogated. Moreover, enforced expression of crystallin αB may induce cisplatin resistance (Volkmann et al. 2013). Similarly, apoptosis-resistant glioblastoma cells may be resensitized to apoptosis inducing agents including TRAIL after targeted inhibition of Crystallin αB (Goplen et al. 2010). Cancer cells reconstituted with a mutant Crystallin αB may inhibit xenografted tumor growth (Kamradt et al. 2005).

## Missing Links of Relationship between TRAIL, PDGF/PDGFR and miRNA in Ovarian Cancer

Confluence of PDGF information suggests categorization on the basis of secretion in its active and inactive forms. As shown in Fig. 4, PDGF-AA, PDGF-AB and PDGF-BB are secreted in an active form. However, PDGF-DD and PDGF-CC are, respectively, activated in the extracellular environment via urokinase plasminogen activator and tissue plasminogen activator, which process CUB domain of PDGF. Binding of PDGF isoforms can autophosphorylating the appropriate PDGF receptor (PDGFR) and downstream oncogenic signaling through receptor which is mediated by JAK/STAT, PI3K, PLC-γ or MAPK signaling pathways. In this section, we provide an overview of how PDGF participates in signaling from, how receptor tyrosine

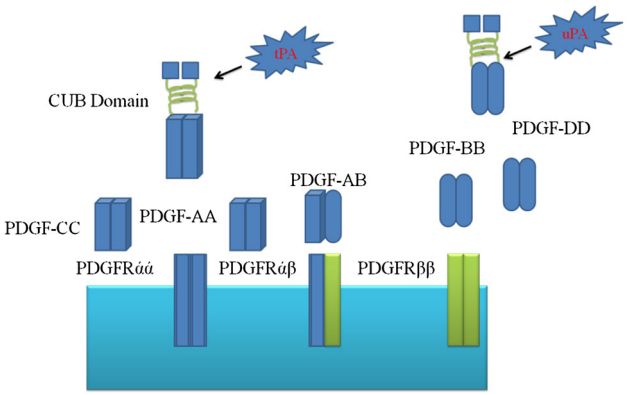


**Fig. 4** Isoforms of PDGF after processing by tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA)

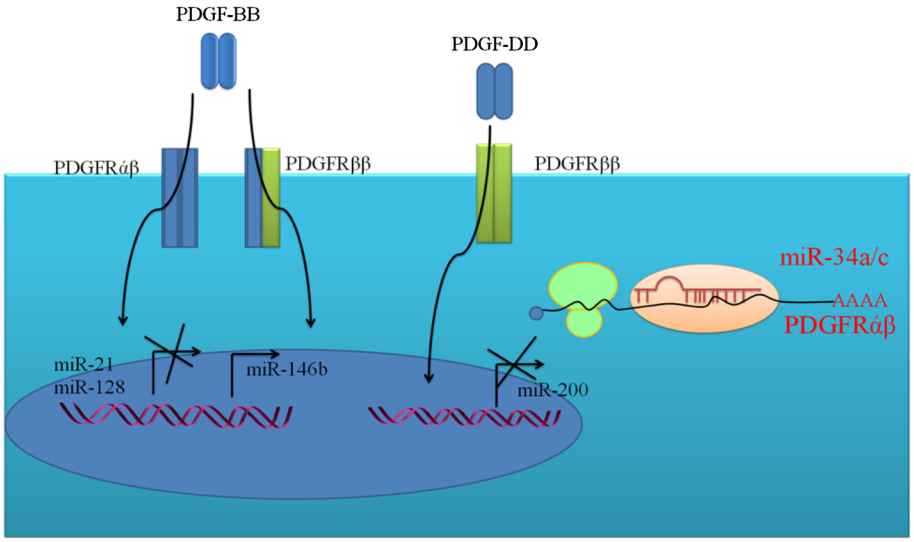


**Fig. 5** miRNA regulation by PDGF signaling axis. Moreover, miRNA controls post-transcriptional processing of PDGFR

kinases (RTKs) in modulating the expression of various subsets of miRNA, and how miRNA, in turn, regulates RTKs to inhibit signaling from growth factor receptors (Fig. 5). Much of our understanding of miRNA regulation by PDGF signaling comes from analyses of in vitro studies. PDGF/PDFGR, miRNA and TRAIL are emerging as new components of a cellular communication network of rapidly increasing complexity.

There are some direct pieces of evidence which underscore misrepresented expression of PDGFR in ovarian cancer. In a study of 170 patients, immunohistochemistry verified 43 % positive for PDGFR-α and 41 % for PDGFR-β in tumor cells (Madsen et al. 2012a). In stromal compartments of chemotherapy-resistant epithelial ovarian cancer patients, it was PDGFR-α (32 %) and PDGFR-β (44 %) using ELISA analysis (Madsen et al. 2012b). Astonishingly, in ovarian granulosa cell tumors PDGFR-α and PDGFR-β stained positive in 100 % (Rocconi et al. 2008). PDGFRs and PDGF-A chain were also found to be frequently expressed in ovarian clear-cell adenocarcinomas (Yamamoto et al. 2008). Circumstantial evidence also provides an overview of serum concentrations of PDGFR-β. PDGFR-β levels were quantified using ELISA and there were notably increased serum levels of PDGFR-β after chemotherapy (Mathey et al. 2013). PDGF-AA and PDGF-BB were overexpressed in ovarian cancer patients.

Regression of tumor growth in tumor models had been well studied. For example, adenoviral expression of a soluble ectodomain of PDGFR-β exhibited a strong activity in the B16-BL6 and CT26.CL25 metastasis models (Kuhnert et al. 2008). PDGFR-β recognizing cyclic peptide (pPB-HSA) conjugated to chemotherapeutic drug was noted to effective against PDGFR-β-expressing cancer cells. Cancer cells treated with geldanamycin may reduce protein contents of PDGFR-α. The results indicated that PDGFR-α was degraded in geldanamycin treated cancer cells and it can be blocked by proteasome inhibitors (Matei et al. 2007a). Invasive potential of ovarian cancer cells can be abrogated by inhibiting PDGF-AA secretion. Upstream regulators of secretory mechanism included ATP-sensitive K(+) channels. RNA interference strategy against K(+) channel resulted in inhibition of PDGF-AA secretion (Yasukagawa et al. 2012). In PDGFR expressing immortalized ovarian cancer cells, PDGF triggered the release of VEGF. PI3K/Akt pathway contributed to PDGF induced secretion of VEGF. Imatinib mesylate (Gleevec) treatment can partially suppress PDGF induced secretion of VEGF (Madsen et al. 2012a; Matei et al. 2007b). Lack of serum levels of PDGF-AA and PDGF-BB in chemotherapy-resistant epithelial ovarian cancer before and during treatment with bevacizumab (Madsen et al. 2012c). A notable efficacy of human-specific monoclonal antibody against PDGFRα (IMC-3G3) in HeyA8-MDR cell line (high PDGFRα expression) was found as compared to SKOV3-ip1 (low PDGFRα expression) (Matsuo et al. 2014).

PDGF-AA represses the expression of let-7d in cancer cells and PDGF-BB stimulates the expression of miR-146b in ovarian cancer cells (Shao et al. 2011). Cancer cells over-expressing PDGF-D displayed notably reduced expression of miR-200. Moreover, stable transfection of miR-200 in cancer cells can restore epithelial phenotype. ZEB1 and ZEB2 are reported to be upregulated and are the known regulators of epithelial to mesenchymal transition (Kong et al. 2009). miR-29b is triggered by GATA in breast cancer cells and negatively regulate PDGF. More importantly, NF-κB and transforming growth factor signaling cascades repress the expression of miR-29b, however, GATA counterbalances inhibitory effects of these signaling cascades on expression of miR-29b (Chou et al. 2013). PDGF-B overexpressing glioblastoma cells

displayed a decrease in miR-21 and miR-128. Gene silencing strategies provided evidence that targeted inhibition of PDGF-B restored the expression of miR-21 and miR-128 (Costa et al. 2012).

Surprisingly it has recently been revealed that PDGFR-α and PDGFR-β are under the control of miR-34a/c. miR-34a/c inhibits lung cancer through targeting of these receptors. It is also encouraging to note that enforced expression of miR-34a/c or gene silencing of PDGFRs resulted in considerably enhanced apoptosis in TRAIL treated non-small-cell lung carcinoma (NSCLC) cells (Garofalo et al. 2013). Seemingly, we still lack near complete information related to PDGF signaling in ovarian cancer cells and how PDGF signaling influences TRAIL mediated signaling in ovarian cancer cells. A better understanding of relationship of PDGF signaling and TRAIL mediated signaling in ovarian cancer cells will be helpful in identifying positive and negative regulators.

## PCR-Based Studies Related to TRAIL

Rapidly accumulating studies have addressed the relationship between biological functionality and genetic variation on a genomic scale. It is noteworthy that application of massively parallel sequencing methods has revolutionized our existing concepts and complemented microarray-based methods. In addition, discovery of smaller structural-variation events has increased exponentially.

Single nucleotide polymorphisms (SNPs) are common variants with high or low penetrances to the disease and cancer phenotypes (Chuang et al. 2008; Erichsen and Chanock 2004). Combined SNP interpretation of intra- and inter-population, clinical and pathological data have helped a lot in developing a broader landscape of a disease phenotype and therapy/treatment (Chen et al. 2013b, 2014; Chuang et al. 2012, 2013; Wu et al. 2013; Yang et al. 2011, 2012, 2013a, b). In this regard, SNPs have taken their place as good candidates for potential biomarkers for disease susceptibility, including various diseases (Chang et al. 2008; Chuang et al. 2014; Lin et al. 2008), cancers (Lin et al. 2009; Yen et al. 2008), treatment response (Chang et al. 2012; Giacomini et al. 2007) and prognosis. Four SNPs located in the 5′ regulatory region (Wang et al. 2000) and three SNPs in the 3′ UTRs of TRAIL gene, located in the 3q26 region (Gray et al. 2001), have been reported. The TRAIL promoter construct with SNP –716 C/T was transiently transfected into HeLa, MCF-7, HepG2, and HT1080 cell lines and the results showed that C allele carriers have higher expression than the T allele carriers. Furthermore, –716 CC genotype carriers had a greater risk of tumorigenesis, however, after establishment of tumor, its progression is likely to be compromised because of higher apoptotic rate (Pal et al. 2011).

Several SNPs of TRAIL gene were also identified in patients with multiple sclerosis (Kikuchi et al. 2005; Weber et al. 2004), fatty liver disease (Yan et al. 2009), breast cancer (Yildiz et al. 2010), prostate cancer (Mi et al. 2011), and colorectal cancer (Yaylım et al. 2012). Apart from being a potential risk factor, confluence of information highlighted potential role of TRAIL variants on cancer prognosis. It is a well-established fact that TRAIL is able to induce apoptosis selectively in cancer cells, both in membrane bound form and soluble form. It is surprising to note that co-culture of lung cancer cells and γδ T cells can induce apoptosis in lung cancer cells. In vitro studies showed that soluble TRAIL (sTRAIL) produced by γδ T cells may induce apoptosis in lung cancer cells through death receptor on their cell surface (Dokouhaki et al. 2013). sTRAIL may be used as a positive marker for apoptosis analysis (Koksal et al. 2008; Shi et al. 2005). SNP 1595 C/T of TRAIL was shown to be significantly associated with tumor stage both in breast (Yildiz et al. 2010) and colorectal cancers (Yaylım et al. 2012). An association for the presence of distant metastasis in serum sTRAIL levels was also found. sTRAIL levels in the colorectal patients with distant metastasis and with C/T genotype for SNP 1595 C/T TRAIL were lower than the controls (Yaylım et al. 2012). It appears that no comprehensive information from existing literature was reported to TRAIL polymorphisms in ovarian cancer. Therefore, the role of TRAIL genetic variants and sTRAIL levels and related genes in ovarian cancer in the disease progression levels should be further evaluated together.

## D-6 and TRA-8

D-6, a monoclonal antibody directed against DR5, exerted growth inhibitory effects on A2780 ovarian cancer cells (Jiang et al. 2012). TRA-8, an agonistic antibody to DR5, has been tested for efficacy in combination with chemotherapeutic drugs in ovarian cancer model. The results revealed that tumor burden was lowest in the group treated with chemotherapy and TRA-8 (Bevis et al. 2011). TRA-8 has also been evaluated for cytotoxic activity in combination with chemotherapeutic drugs in an ex vivo human ovarian cancer model (Frederick et al. 2009).

## Clinical Trials

There is a recent clinical trial reporting use of mapatumumab in combination with paclitaxel and carboplatin

in NSCLC patients. No improvements in response or disease control rates, progression-free survival, or overall survival were noted upon combining mapatumumab with paclitaxel and carboplatin (von Pawel et al. 2014). Mapatumumab has previously been tested in phase I, open-label, and dose-escalation study to assess the tolerability and toxicity profile. One patient had a diagnosis of borderline ovarian carcinoma and she experienced slow progression before entering into study and received 33 cycles of mapatumumab. Out of nine ovarian cancer patients, one cancer patient had a static disease (Hotte et al. 2008). Dose-limiting toxicity was observed in a 54-year-old ovarian cancer patient with multiple liver metastases. The patient had elevated levels of hepatic transaminase after the first dose of PRO95780, a human IgG1 monoclonal antibody directed against DR5. There was a 23 % reduction in a measurable disease after eight cycles of PRO95780 (Camidge et al. 2010).

## Conclusion

Phenotypic plasticity and generation of drug resistant subpopulation of cells are two important mechanisms that add another layer of complexity to standardization of therapy in ovarian cancer cells. These mechanisms reconstitute the antigenic landscape of tumor cells, rewire oncogenic signaling networks, protect against cell death and reprogrammed immune cell functions including transcriptional repression of TRAIL and DR. There is a rapid progress in understanding genetic heterogeneity in recent years which has been observed between patients from different geographical and ethnic populations, different individuals within these populations and unfortunately treatment of patients with ovarian cancer continues to be challenging. TRAIL mediated signaling has emerged as an important signaling pathway in inducing apoptosis in cancer cells. However, mutations in different genes, loss of tumor suppressors, and overexpression of anti-apoptotic proteins may substantially contribute in abrogating TRAIL mediated apoptosis in cancer cells. Moreover, nonavailability of death receptors at cell surface of cancer cells is another challenge that is being investigated extensively. Furthermore, miRNA regulation of TRAIL mediated signaling is incompletely studied that adds another layer of intricacy. Moreover, PDGF signaling may contribute to ovarian cancer development but in depth analysis of this particular signaling is necessary for targeted therapy. It is becoming clear that opportunities identified in the molecular microcosm of carcinogenesis pathways discover many promising targets and identification of drugs with minimal off target effects will be helpful in limiting ovarian cancer.

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