

# Elucidation for modulation of death receptor (DR) 5 to strengthen apoptotic signals in cancer cells

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**Abstract** The tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) induces apoptosis via death receptor (DR) 4 or DR5 preferentially in cancer cells, and not in normal cells with relatively high decoy receptor expression. However, multiple mechanisms in cancer cells induce resistance to DRs-mediated apoptosis. Therefore, understanding of molecular mechanisms for resistance to DRs-mediated apoptosis can find the strategy to increase sensitivity. Although multiple proteins are involved in resistance to DRs-mediated apoptosis, we focus on modulation of DR5 to overcome resistance. Here, we discuss regulation of DR5 expression or activation by epigenetic modification, transcription factor at the transcriptional levels, micro RNA and RNA-binding proteins at the post-transcriptional levels, and ubiquitination and glycosylation at the post-translational levels. In addition, we also mention about relationship between localization of DR5 and death signaling activation. The purpose of this review is to help understand relationship between regulatory mechanisms of DR5 and resistance to TRAIL or DRs-targeted agonist monoclonal antibodies, and to develop innovative anti-cancer therapies through regulation of DR5 signaling.

**Keywords** TRAIL · Death receptor · Expression · Localization · Apoptosis

## Introduction

Apoptosis, a form of cell death in which a programmed sequence of events, is most frequent cell death mode induced by anti-cancer drugs in cancer cells. The tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) induces apoptosis via death receptors (DRs), DR4 or DR5, in cancer cells. In contrast, since normal cells highly express decoy receptors (DcRs), which are partially or completely lack of functional death domain (DD), ligation of TRAIL fails to induce cell death. Underlying mechanism of TRAIL-induced apoptosis is that ligation of TRAIL induces oligomerization of DRs, and Fas-associated protein with death domain (FADD) binds to DD of DRs. Death-inducing signaling complexes (DISCs) for extrinsic apoptosis are composed of DRs, cytosolic adaptor FADD, and pro-caspase-8/cFLIP. Assembly of DISC is accomplished by interaction of DDs and death effector domains (DEDs). Procaspase-8 is recruited to DED of FADD, and then multiple procaspase-8 is assembled through DED of caspase-8. DISC formation is critical for activation of caspase-8 via cleavage of procaspase-8, and then activates effector caspases, such as caspase-3, 6, and 7, leading to induction of apoptosis in type 1 cells (Mahalingam et al. 2009). Mitochondrial pathway could be involved in TRAIL-mediated apoptosis in type 2 cells. When caspase-8 truncates Bid, it is oligomerized with Bak and Bax which induces mitochondrial membrane permeabilization. Cytochrome *c* released from mitochondria forms apoptosome with Apaf-1, which provide platform for recruitment and activation of procaspase-9. Activated caspase-9, like a caspase-8, triggers apoptosis via activation of effector caspases (Mahalingam et al. 2009). As mentioned above, ligation of TRAIL with DRs produces the first signal to induce apoptosis in both type 1 and type 2

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cells. Therefore, dysregulation of expression and localization of DRs are resistant to TRAIL.

DR5 gene located on chromosome 8p (MacFarlane et al. 1997), and DR5 has two splice variants, long and short DR5, which is absence of 29 different amino acids in the extracellular region (Mert et al. 2017). Interestingly, Van Roosmalen et al. (2014) reviewed about DRs preference for TRAIL-induced apoptosis. These results are derived from experiments which used single recombinant TRAIL, DR4- (Tur et al. 2008), and DR5-selective TRAIL variants (van der Sloot et al. 2006). According to their research, TRAIL has different sensitivity to DRs-induced apoptosis depending on cancer cell lines. For examples, leukemic cells have a preference for DR4-induced apoptosis, and lymphoma, myeloma, and most solid tumor shows heterogeneity. In addition, Truneh et al. reported that TRAIL binding affinity to DR5 is the strongest at 37 °C, compared with other DRs and DcRs (Truneh et al. 2000). There are various mechanisms for inducing TRAIL resistance, but we discuss about enhancement of DRs-mediated apoptosis via modulation of human DR5.

## Modulatory mechanisms of DR5 expression

### Transcriptional regulation

#### *Sp1 (specificity protein 1)*

Sp1 activates the transcription by binding CG-rich Sp-binding sites in promoter of genes, which are related with cell growth, differentiation, apoptosis, and carcinogenesis (Vizcaino et al. 2015). DR5 is one of Sp1-regulated genes. DR5 promoter contains minimal promoter element at -198 to -166, which region also overlap with two Sp1 binding sites. These two Sp1 sites play a critical role in basal transcription activity of DR5 (Yoshida et al. 2001). In addition, anti-cancer drugs induced DR5 expression in a Sp1-dependent manner. For examples, deoxycholic acid and sodium butyrate increase DR5 expression via Sp1 transcriptional activation (Higuchi et al. 2004; Kim et al. 2004). Quercetin (3',3',4',5,7-pentahydroxyflavone), a flavonoid found in fruits and vegetables, also increases Sp1-mediated DR5 expression (Kim et al. 2008). Beta-lanone, butein, piceatannol, and capsaicin sensitize TRAIL-mediated apoptosis via up-regulation of Sp1-mediated DR5 expression (Kim et al. 2010; Moon et al. 2010, 2012; Kang et al. 2011). Notch is important signaling molecules in tumorigenesis by modulation of cell differentiation, proliferation and death in cancer cells. Recently, inhibition of notch1 signaling enhances TRAIL-mediated apoptosis in glioblastoma, and these mechanisms are related with up-

regulation of DR5 by JNK-mediated Sp1 activation (Fassl et al. 2015).

#### *p53*

p53 is mortal of cellular growth, division and proliferation by regulation of cell cycle arrest and apoptosis. In the initial study, p53 status seems not to be important in TRAIL-induced cell death. Since p53 status is mutated in a half of cancer cells, p53-independant cell death by TRAIL seems attractive. However, Wu et al. reported that DR5 is a DNA damage-inducible p53-regulated gene (Wu et al. 1997). DR5 is identified as a transcript induced by anti-cancer drugs including doxorubicin (Lowe et al. 1993), and doxorubicin activates p53-dependent signaling pathway. Therefore, Wu et al. hypothesized that DR5 is a gene controlled by p53, and found that doxorubicin increases DR5 expression in p53 wild-type cells, but not p53-mutated cells (Wu et al. 1997). The binding sites (BS) of p53 transcription factor were identified three sites in DR5 promoter region. There are BS1, BS2, and BS3, and they are located - 0.82 Kb, + 0.25 Kb (within Intron 1), and + 1.25 Kb (within Intron 2) of the ATG site, respectively. Among them, BS2 has critical roles on p53-dependent DR5 expression (Takimoto and El-Deiry 2000). Anti-cancer drugs [etoposide, CPT-11 (Wang and El-Deiry 2003), and nutlin-3 (Hori et al. 2010)] or ionizing radiation (Sheikh et al. 1998) increase DR5 mRNA expression in a p53-dependent manner.

#### *CHOP (CCAAT/enhancer-binding protein homologous protein)*

CHOP is endoplasmic reticulum (ER) stress-induced a major transcriptional factor. CHOP induces ER-stress-mediated apoptosis depending on duration and severity of ER stress (Oyadomari and Mori 2004). ER stress inducers, including thapsigargin and tunicamycin, induce DR5 expression, and CHOP as a transcription factor plays critical roles on DR5 expression (Yamaguchi and Wang 2004; Shiraishi et al. 2005). Yamaguchi and Wang (2004) identify the CHOP binding element in the DR5 promoter between - 276 and - 264 (+ 1 represents the translation start site). Proteasome inhibitor (MG132) (Yoshida et al. 2005), farnesyltransferase inhibitor (Sun et al. 2007), silibinin (Son et al. 2007), and 15-deoxy- $\Delta$ 12, 14-prostaglandin J<sub>2</sub> (15d-PGJ<sub>2</sub>) increases CHOP-dependent DR5 transcription (Su et al. 2008). In addition, adverse effect in a cardiovascular or anti-cancer effect of cyclooxygenase-2 (COX-2) inhibitor (celecoxib and ON09310) is related with CHOP-dependent DR5 expression in a COX-2 independent manner, followed by cell death (He et al. 2008). Interestingly, although IRE1 $\alpha$ , as an unfolded protein response

(UPR) sensor transiently triggers decay of DR5 mRNAs, persistent ER stress increases CHOP-dependent DR5 expression. Up-regulated DR5 induces TRAIL-independent apoptosis via caspase-8 (Lu et al. 2014). In contrast, Glab et al. reported that ER stress by thapsigargin, tunicamycin, or subtilase cytotoxin triggers apoptosis in a DR5-independent manner, and Bim is more important on ER-stress induced cell death (Glab et al. 2017). Therefore, ER stress could increase DR5 expression via CHOP, but roles of DR5 on ER stress-induced apoptosis are controversial.

#### *NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells)*

NF-κB is composed of five Rel family members (RelA/p65, RelB, c-Rel, p50, and p52). In canonical pathways, IκB kinase (IKK) activation by stimuli induces phosphorylation and degradation of IκB. Released NF-κB dimer (predominantly p65/p50) from IκB translocate into nucleus. In non-canonical pathway, NF-κB-inducing kinase (NIK) induces activation of IKKα, and then phosphorylates p100, followed by processing of p100. Generated p52 from p100 binds RelB, and then translocates into the nucleus (Sun 2011). The function of NF-κB in cancer is controversial, depending on cell types, stimuli, and regulated genes. NF-κB signaling is also involved in DR5 expression. Among NF-κB subunits, c-Rel is a critical for DR5 transcription (Ravi et al. 2001). TRAIL induces apoptosis in RelA<sup>-/-</sup> or wild-type mouse embryonic fibroblast (MEF), but not c-Rel<sup>-/-</sup> MEF, which are absence of DR5 expression. Although c-Rel activation by TNF-α increases DR5 expression, RelA is also induces anti-apoptotic proteins, such as Bcl-xL, resulted in inhibition of apoptosis by TRAIL (Ravi et al. 2001). In addition, overexpression of RelA inhibits DR5 expression, whereas overexpression of c-Rel enhances DR5 expression in TRAIL-treated cells (Chen et al. 2003). The subunit of NF-κB has difference preferences, depending on consensus sequence of target genes (Baeuerle and Baltimore 1996). Proteasome inhibitor, apple procyanidins, Smac mimetics, and hepatitis B virus X (HBx) protein increase DR5 expression via NF-κB activation (Chen et al. 2008; Maldonado et al. 2010; Eckhardt et al. 2013; Kong et al. 2015). Furthermore, knock down of death-associated protein kinase 2 (DAPK2) by siRNA induces NF-κB transcriptional activity, leads to the induction of DR5 expression (Schlegel et al. 2014). It reported that NF-κB binding site lies between + 385 and + 394 in the first intron of DR5 (Yoshida et al. 2001). However, NF-κB is also key signaling molecules to induce anti-apoptotic proteins, thus the role of NF-κB in DRs-mediated apoptosis must be carefully mentioned.

#### *YY1 (Yin Yang 1)*

YY1 is a 65 kDa of zinc finger transcription factor and modulates transcriptional activity of gene promoter as activator or repressor depending on interacting proteins, such as a histone deacetylases (HDAC) and a histone acetyltransferases (HAT) (Thomas and Seto 1999). In case of DR5, YY1 acts as a repressor. The binding site for the YY1 is localized between - 804 and - 794 in the promoter of DR5 (Yoshida et al. 2001; Baritaki et al. 2007a), and multiple chemotherapeutic drugs, including cisplatin, etoposide, adriamycin and vincristine, increase DR5 expression through inhibition of YY1 expression and transcriptional activity (Baritaki et al. 2007a). In addition, Raf-1 kinase inhibitor protein (RKIP) inhibits NF-κB activity, followed by inhibition of YY1 expression (Baritaki et al. 2007b). Since NF-κB directly or indirectly regulates YY1 expression (Baritaki et al. 2007a, b; Wang et al. 2007), the novel proteasome inhibitor (NPI-0052) also inhibits NF-κB activity by accumulation of p-IκB, and sequentially induces up-regulation of DR5 expression through inhibition of YY1 expression and transcriptional activity (Baritaki et al. 2008). In addition, nitric oxide (Huerta-Yepez et al. 2009) and BH3-mimetics obatoclax also sensitizes TRAIL-induced apoptosis through up-regulation of DR5 expression by inhibition of YY1 transcriptional activity (Martinez-Paniagua et al. 2011).

#### *Others*

Other transcriptional factors are also involved in DR5 expression. For examples, epithelium-specific Ets factor, family member 3 (ESE-3) increases DR5 expression by binding to purine-rich GGAA/T sequences in cooperation with CBP and p300 (Lim et al. 2006), and activating transcription factor 3 (ATF3) is a transcriptional factor for DR5 induction through ROS-ER stress pathways (Edagawa et al. 2014). In contrast, nuclear Bcl-2 nineteen kilodalton interacting protein (BNIP3) binds to the DR5 promoter, and then decreases DR5 expression (Burton et al. 2013).

#### **Epigenetic modification**

##### *Methylation*

DNA methylation is important on chromatin remodeling and gene expression, and DNA methyltransferases (DNMTs) induce cellular DNA methylation (Li et al. 2013). To identify the roles of methylation enzymes (DNMT1 and DNMT3b) in cell survival, expression of both are blocked by siRNA in human hepatocellular carcinoma cells. Double knock-down of DNMT1 and DNMT3b by siRNA increased TRAIL-treated cell death

via up-regulation of DR5 mRNA and protein expression (Kurita et al. 2010). However, alteration of methylation in DR5 promoter is not detected. Therefore, TRAIL sensitization by inhibition of methylation is indirectly related with up-regulation of DR5 expression.

Histone lysine demethylase 4A (KDM4A) is a member of the Jumonji C domain-containing KDM4 subfamily of histone demethylase, which induces demethylation of histone H3 on lysine 9 and 36, and histone H1.4 on lysine 26 (Berry and Janknecht 2013). Recently, Wang et al. reported that inhibition of KDM4A induces DR5 mRNA and protein expression and enhances apoptosis in cancer cells. However, KDM4A did not directly bind to the promoter of DR5, and indirectly increases association of histone modifying enzyme complexes in promoter of CHOP expression, resulted in induction of DR5 expression (Wang et al. 2016). Since there is very little methylation in the DR5 promoter (van Noesel et al. 2002), there seems to be difficult in finding direct links between the demethylation and DR5.

### Acetylation

Acetylation and deacetylation of lysine residues in nucleosomal histones is regulated by histone acetyltransferase and histone deacetylase (HDACs), respectively. Hyper-acetylation of lysine residues in nucleosomal histones increases or restores gene expression, which is associated with cell cycle arrest, cell death, and differentiation. For this reason, HDAC inhibitors are recognized as a target of cancer therapy (Newbold et al. 2016). LAQ824, a HDAC inhibitor, sensitizes TRAIL-induced apoptosis in human acute leukemia cells. The molecular mechanism of LAQ824-induced TRAIL sensitization is associated with up-regulation of DR5 mRNA and protein expression. LAQ824 acetylates histones H3 and H4 in DR5 promoter, resulted in induction of DR5 expression and DISC formation (Guo et al. 2004). In addition, depletion of HDAC2, not HDAC1, and HDAC inhibitors [trichostatin A (TSA), sodium butyrate, and suberoylanilide hydroxamic acid (SAHA)] increase TRAIL-induced apoptosis in cancer cells, but they did not show the acetylation of nucleosomal histones in DR5 gene (Nakata et al. 2004; Schuler et al. 2010). Therefore, modulation of nucleosomal histones acetylation using HDAC inhibitors could sensitize TRAIL-mediated apoptosis through up-regulation of DR5 expression.

### Post-transcriptional regulation

#### *RNA-binding protein HuR*

The stability of mRNAs is regulated by binding of mRNA binding proteins in the adenylate-uridylylate (AU)-rich

elements in the 3'-untranslated region (UTR). It has been known that the stability of DR5 mRNA is also modulated by several stimuli. For examples, the 15d-PGJ<sub>2</sub> (Nakata et al. 2006) and thapsigargin (He et al. 2002) induces DR5 expression via stabilization of DR5 mRNA. The 3'UTR and 5'UTR of human DR5 gene has AU-rich elements. Kandasamy et al. identify the specific sequences, which are critical for DR5 mRNA stability (Kandasamy and Kraft 2008), and it is the AU-rich element from 3556 to 3587 in the 3'UTR region of human DR5 gene. Among mRNA binding proteins, only HuR binds to this AU-rich element, leads to stabilization of DR5 mRNA by proteasome inhibitor (PS-341) in LNCaP human prostate cancer cells, but not PC-3 and DU145 (Kandasamy and Kraft 2008). In addition, chloroquine also increases DR5 mRNA stability in human renal carcinoma Caki cells, but HuR is not involved (Park et al. 2016). In contrast, Pineda et al. reported that DR5 agonist induces cleavage and translocation from nucleus to cytoplasm of HuR, and then binding of HuR to 5'UTR by DR5 agonist inhibits DR5 translation in pancreatic cancer cells (Pineda et al. 2012).

#### *MicroRNA(miR)-1246 and miR-133a*

MicroRNAs are small endogenous noncoding RNA (~ 22 nucleotides), which reduces mRNA stability or inhibit translation by binding in 3'UTR of target mRNA target genes (Filipowicz et al. 2008). The miR-1246 released from irradiated cancer cells moves to recipient cells in an exosome independent manner, and induces proliferation and radio-resistance of irradiated recipient cells. They found that DR5 is direct target of miR-1246, which represses mRNA and protein expression of DR5. Extracellular miR-1246 by radiation has bystander effects, which are related with resistance in surrounding cells (Yuan et al. 2016). Although they did not investigate whether miR-1246 is involved in TRAIL resistance, the relationship between the two is predictable. However, it needs to prove through accurate experiments. In addition, miR-133a also modulates DR5 expression in glioblastoma. miR-133a suppresses DR5 expression directly by binding in 3'UTR of DR5, which is related with TRAIL resistance (Wang et al. 2017).

#### *Others*

Zhang et al. reported that levels of DR5 protein expression is critical roles on TRAIL sensitivity in multiple melanoma cells, since between mRNA and protein levels of DR5 has no correlation (Zhang et al. 2004). They identified the reason as a difference in regulation of translation. Luciferase activity with 3'UTR of DR5 in TRAIL-resistance cells was suppressed compared with that in TRAIL-

sensitive cells, and a 23 base (TAAATGCTTTATTTATTT ATTTG) in AU-rich element of 3'UTR plays critical roles in translation of DR5 in TRAIL-treated cells. Although specific RNA binding proteins were not identified, at least this response is independent of HuR and HuD (Zhang et al. 2004). Therefore, studies are not enough to understand the regulatory mechanism of mRNA stabilization and translation of DR5. Modulation of DR5 mRNA stability and translation might be dependent of cell types, stimulator, RNA binding proteins and binding sites.

## Post-translational regulation

### Ubiquitination

Ubiquitination to the target proteins can change protein stability and functions and is mediated by three enzymes, such as E1 (ubiquitin activation), E2 (ubiquitin conjugation), and E3 (ubiquitin ligase) (Hershko and Ciechanover 1998). DR5 is also regulated by ubiquitin–proteasome pathway, and proteasome inhibitors (PS-341, MG132, and epoxomicin) increase DR5 protein expression, resulted in enhancement of TRAIL-mediated apoptosis (He et al. 2004; Liu et al. 2007). Recently, Song et al. reported that c-Casitas B-lineage lymphoma (Cbl) induces degradation of DR5 in TRAIL-treated cells (Song et al. 2010). Cbl is a multi-adaptor protein. c-Cbl, Cbl-b, and Cbl-c (Cbl-3) are identified. Cbl-b and c-Cbl have E3 ligase activity (Thien and Langdon 2005), both Cbls regulate DR5 expression. The c-Cbl binds to DR5 and induces degradation of DR5 in TRAIL-treated cells, resulted in the early phase of acquired TRAIL resistance (Song et al. 2010). In addition, bufalin is a major active ingredient of the traditional Chinese medicine ChanSu, increases DR5 expression via down-regulation of Cbl-b expression (Yan et al. 2012), and shRNA-expressing adenovirus against c-Cbl also enhances TRAIL-mediated apoptosis through induction of DR5 expression (Kim et al. 2013). Although there is not direct deubiquitinase (DUB) of DR5, the DUB also controls the expression of DR5. b-AP15 blocks ubiquitin-specific protease (USP)14 and ubiquitin carboxyl-terminal hydrolase L (UCHL) 5, which are 19S regulatory particle-associated DUBs, followed by accumulation of the ubiquitin conjugated proteins via inhibition of proteasomal function (D'arcy and Linder 2012). DR5 accumulated by b-AP15 sensitized TRAIL-mediated apoptosis (Oh et al. 2017). Therefore, ubiquitin–proteasome pathway is involved in modulation of DR5 protein expression.

### Glycosylation

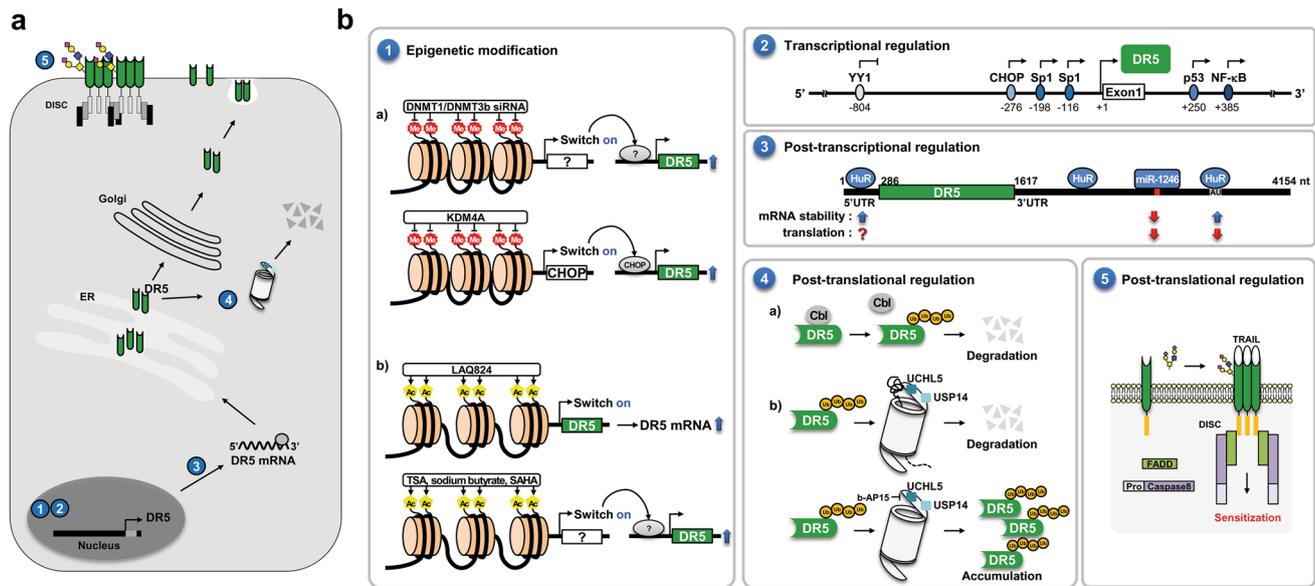
Glycosylation is a common post-modification that occur more than 50% of proteins, and is known to control not

only protein folding but also the ability to signaling transduction by proteins. DR5 also occurs with *O*-glycosylation, which increases TRAIL-mediated apoptosis. *O*-glycosylation is mediated by *N*-acetyl-galactosamine (GalNAc) and *N*-acetyl-glucosamine (GlcNAc). Wagner et al. reported that sensitivity to TRAIL is correlated with levels of *O*-glycosyltransferase by *N*-acetyl-galactosamine transferase (GALNT)14 or GALNT3 with *O*-glycan processing enzymes fucosyltransferases (FUT) 3 and FUT6 depending on cell types (Wagner et al. 2007). DR5 is *O*-glycosylated on two stretches of serine and threonine in front of cysteine rich domains (CRD) 2 and within CRD2 and CRD3 (Micheau 2018). Interestingly, glycosylation of DR5 has no effect on TRAIL binding affinity and DR5 cell surface expression, and promotes receptor clustering and DISC formation. Furthermore, they identify that Ser201 is a primary modification site in DR5. Based on these results, Howard et al. reported that immunocytochemistry assay to detect GALNT14 and FUT3/6, but not GALNT3, can be used to distinguish patients, who have effectiveness in dulcanermin- and drozitumab-based therapy (Stern et al. 2010). *O*-GlcNAcylation of DR5 by GlcNAc induces DR5 clustering and DISC formation, resulted in enhancement of TRAIL-induced apoptosis in non-small cell lung cancer cells (Liang et al. 2018). We summarized the molecular mechanisms and published papers that regulate expression and activation of DR5 (Fig. 1 and Table 1).

## Modulation of DR5 localization

### Lipid rafts

It has been well-known that ceramide converts raft domain in membrane into larger domains (lipid raft domains, glycosphingolipid-enrich domains or ceramide-enriched domains), which are important on initiation of receptor-specific signaling via clustering, re-organization of signaling molecules, amplification of signal, and exclusion of inhibitory signals and, thus, amplify a receptor-mediated signals (Bollinger et al. 2005; Grassme et al. 2007). Like other receptor-mediated signaling, localization of DR5 in lipid raft is important on induction of TRAIL-mediated apoptosis. Sensitivity of leukemia to TRAIL-induced apoptosis is determined by recruitment of DISC components including DR5 to the lipid raft (Min et al. 2009). In addition, reactive oxygen species-dependent acid sphingomyelinase activation by TRAIL induces ceramide release, regulated in induction of ceramide-enriched domains in plasma membrane. Clustering of DR5 in these domains plays critical roles in TRAIL-mediated apoptosis (Dumitru and Gulbins 2006). In addition, the importance of DR5 clustering in lipid raft domains in TRAIL-induced apoptosis has been reported in many studies. For examples,



**Fig. 1** Modulatory mechanisms of DR5 expression and activation to enhance DRs-mediated apoptosis signaling. **a** Summary for control mechanism of DR5. **b** Modulatory mechanism of activation and expression of DR5. Expression of DR5 is directly or indirectly regulated by methylation and acetylation, and multiple transcription factors and RNA-binding proteins also increase or decrease DR5 expression depending on regulatory proteins and binding sites. In addition, expression and clustering of DR5 are modulated by ubiquitin–proteasome pathway and glycosylation

inhibition of COX-2 enhances TRAIL-induced apoptosis through clustering of DR5 and DISC components in ceramide-enriched caveolae (Martin et al. 2005), and DR5 clustering in lipid rafts is a mechanism of TRAIL sensitization by doxorubicin (Dumitru et al. 2007), ursodeoxycholic acid (Lim et al. 2011), oxaliplatin (Xu et al. 2009), and synthetic alkyl-lysophospholipids (ALPs) (Gajate and Mollinedo 2007). Interestingly, c-Cbl and Cbl-b also inhibit localization of DR5 in lipid rafts (Xu et al. 2009). In contrast, ceramide synthase 6 and exogenous ceramide increase TRAIL sensitivity (Voelkel-Johnson et al. 2005; White-Gilbertson et al. 2009).

#### Cytosolic localization by endocytosis

Before TRAIL is incorporated into the DRs, the endocytosis of DRs is sufficient to provide resistance to TRAIL (Zhang and Zhang 2008; Chen et al. 2012b), and it has been known that endocytosis of receptor is not required for TRAIL-induced apoptosis in Burkitt lymphoma B cell line (Kohlhaas et al. 2007). However, Austin et al. (2006) reported about positive feedback mechanism of TRAIL-induced apoptosis with regard to endocytosis in TRAIL-sensitive cells. DR5 activation by TRAIL induces cleavage of adaptor protein (AP)2 $\alpha$ , AP1/2 $\beta$ , and clathrin heavy chain (CHC), which are machinery of clathrin-dependent endocytosis, and attenuates DR5 endocytosis, leading to amplification of TRAIL-induced apoptosis signaling. In

contrast, clathrin-dependent endocytosis is critical for TRAIL-induced apoptosis via lysosomal membrane permeabilization in hepatocellular carcinoma (Akazawa et al. 2009). TRAIL triggers endocytosis of DR5, and DR5 with trafficking to lysosomal membrane induces release of cathepsin and apoptosis. Inhibition of endocytosis by dominant negative dynamin blocks TRAIL-induced apoptosis via inhibition of endocytosis (Akazawa et al. 2009). Therefore, so far, the role of endocytosis in DRs-mediated apoptosis is unclear.

#### Autophagosome

The role of autophagy in cell death is controversial, and expression of DR5 by autophagy is also dependent of stimulators. Gefitinib and ginsenoside compound K increase DR5 expression and inhibition of autophagy reduces DR5 expression in human colon cancer cells (Chen et al. 2016a, b). In contrast, telmisartan, a drug for hypertension, causes induction of DR5 via inhibition of autophagy (Rasheduzzaman et al. 2018). However, there is no direct mechanism how autophagy controls the expression of DR5. Therefore, we only discuss about direct regulation of DR5 expression by autophagy. Di et al. found that the sensitivity to TRAIL negatively correlated with LC3 II in multiple breast carcinomas, and DR5 is localized in autophagosomes in TRAIL-resistance cells. When autophagy is inhibited by knock-down of ATG7, beclin-1,

**Table 1** Drugs that control DR5 expression and activation

Target	Effect on DR5 expression/activation
Treatment	Reference
<b>1. Transcriptional regulation</b>	
Sp1	Increase
Beta-lanone	(Kim et al., 2010)
Butein	(Moon et al., 2010)
CaM antagonists (Trifluoperazine, Tamoxifen)	(Yuan et al., 2015)
Capsaicin	(Moon et al., 2012)
8-Chloro-adenosine	(Sun et al., 2008)
Deoxycholic acid	(Higuchi et al., 2004)
Hepatitis C Virus	(Deng et al., 2012)
PARP inhibitors (Olaparib, Veliparib)	(Meng et al., 2014)
Piceatannol	(Kang et al., 2011)
Quercetin	(Kim et al., 2008)
Silibinin	(Dilshara et al., 2018)
Sodium butyrate	(Kim et al., 2004)
Thioredoxin reductase inhibitor (DTCD)	(Lin et al., 2013)
<b>p53</b>	
Apigenin	(Chen et al., 2016c)
CPT-11	(Wang and El-Deiry, 2003)
Doxorubicin	(Lowe et al., 1993; Wu et al., 1997; Das et al., 2017)
Etoposide	(Wang and El-Deiry, 2003; Das et al., 2017)
Fisetin	(Min et al., 2017)
5-Fluorouracil	(Kuribayashi et al., 2011; Akpınar et al., 2015)
Ionizing radiation	(Sheikh et al., 1998)
Kaempferol	(Lee et al., 2016)
Nutlin-3	(Hori et al., 2010; Meijer et al., 2013; Urso et al., 2017; Surget et al., 2012)
Proteasome inhibitor (MG132)	(Chen et al., 2008)
Triptolide	(Sun et al., 2017; Carter et al., 2008; Xiaowen and Yi, 2012)
<b>CHOP</b>	
Adenylyl cyclase inhibitor (MDL-12330A)	(Lim and Han, 2017)
Amiodarone	(Kim et al., 2011)
C-27-carboxylated oleanolic acid (C27OA-1)	(Sun Byun et al., 2018)
Carnosic acid	(Jung et al., 2015)
COX-2 inhibitor (Celecoxib and ON09310)	(He et al., 2008)
Farnesyltransferase inhibitor (Lonafarnib)	(Sun et al., 2007)
Fenretinide	(Kouhara et al., 2007)
Ferroptosis-inducing agents	(Lee et al., 2018)
Guggulsterone	(Moon et al., 2011)
Hsp90 inhibitor (17-AAG)	(Yao et al., 2017)
Isoobtusilactone A	(Chen et al., 2012a)
Neddylation inhibitor (MLN4924)	(Chen et al., 2016d)
15d-PG <sub>2</sub>	(Su et al., 2008)
Proteasome inhibitor (MG132, Ixazomib, Nelfinavir)	(Yoshida et al., 2005; Yue and Sun, 2018; Tian et al., 2011)

**Table 1** continued

Rottlerin	(Lim et al., 2009)
RU486	(Min et al., 2012)
Silibinin	(Son et al., 2007)
Simvastatin	(Gopalan et al., 2013)
Steroidal saponin (20(S)-ginsenoside Rg3)	(Lee et al., 2013)
Thapsigargin	(Yamaguchi and Wang, 2004)
mTOR inhibitors (Everolimus, Temsirolimus)	(He et al., 2016)
Tunicamycin	(Shiraishi et al., 2005; Guo et al., 2017)
Verrucarin A	(Moon et al., 2013)
Withaferin A	(Lee et al., 2009)
YM155	(Pennati et al., 2015)
<b>NF-κB</b>	
Increase	
Hepatitis B Virus X protein	(Kong et al., 2015)
Proteasome inhibitor (MG132)	(Chen et al., 2008)
Smac mimetic (BV6)	(Eckhardt et al., 2013)
<b>YY1</b>	
Decrease	
BH3 mimetics (Obatoclax)	(Martinez-Paniagua et al., 2011)
Chemotherapeutic drugs	(Baritaki et al., 2007a)
Chimeric anti-CD20 mAb (Rituximab)	(Bonavida, 2007)
Nitric oxide donor (DETANONOate)	(Huerta-Yepez et al., 2009)
Proteasome inhibitor (NPI-0052)	(Baritaki et al., 2008)
RKIP	(Baritaki et al., 2007b)
Saquinavir-NO	(Donia et al., 2011)
<b>2. Epigenetic modification</b>	
<b>Methylation</b>	
Increase (Indirect)	
Double knock-down of DNMT1/DNMT3b	(Kurita et al., 2010)
Knock-down of KDM4A	(Wang et al., 2016)
<b>Acetylation</b>	
Increase (direct or indirect)	
HDAC inhibitor (LAQ824)	(Guo et al., 2004)
HDAC inhibitors (SAHA, TSA, Sodium butyrate)	(Nakata et al., 2004)
Knock-down of HDAC2	(Schuler et al., 2010)
<b>3. Post-transcriptional regulation</b>	
<b>HuR</b>	
mRNA stability increase	
DR5 agonist (Gemcitabine)	(Pineda et al., 2012)
Proteasome inhibitor (PS-341)	(Kandasamy and Kraft, 2008)
<b>miR-1246</b>	
mRNA stability decrease	
miR-1246 mimetic	(Yuan et al., 2016)
<b>4. Post-translational regulation</b>	
<b>c-Cbl</b>	
Decrease	
Bufalin	(Yan et al., 2012)
Chloroquine	(Park et al., 2016)
Knockout of c-Cbl	(Kim et al., 2013)
<b>USP14 &amp; UCHL5</b>	
Increase	
b-API5	(Oh et al., 2017)
<b>O-glycosylation</b>	
Increase receptor clustering/DISC formation	
Overexpression of GALNT14	(Wagner et al., 2007)
N-acetyl-glucosamine	(Liang et al., 2018)

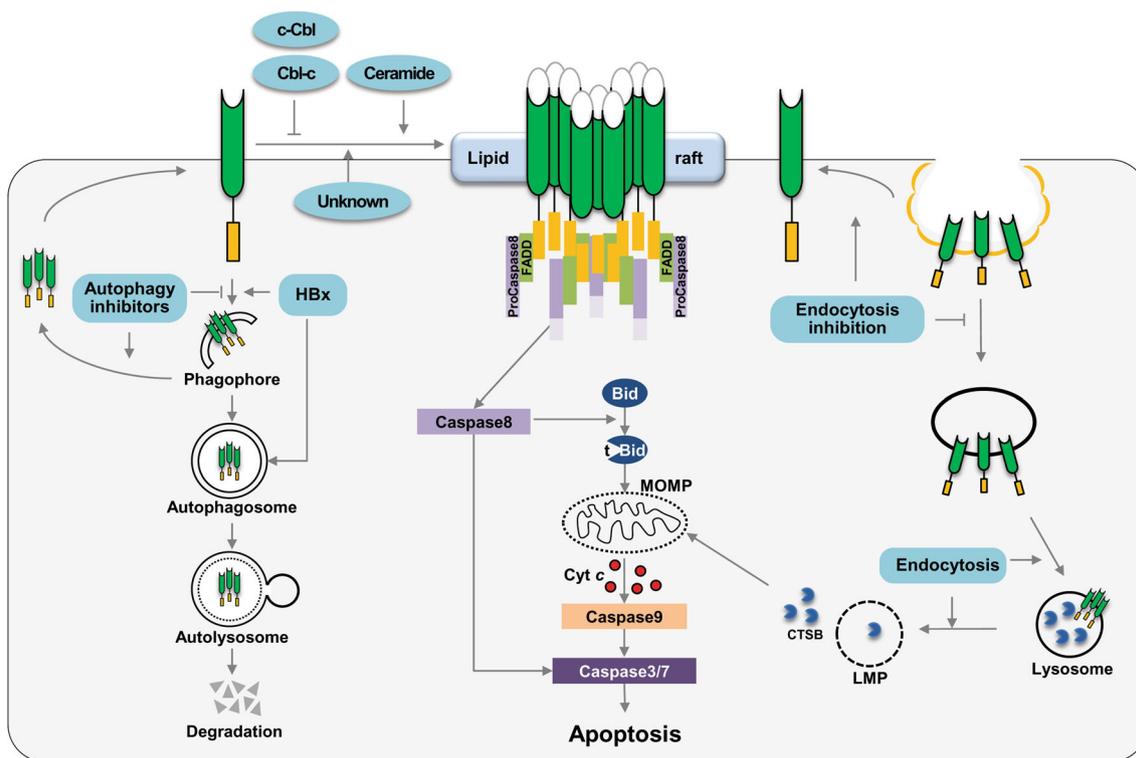
**Table 1** continued

*CaM* Calmodulin, *PARP* Poly(ADP-ribose) polymerase, *KDM4A* Histone lysine demethylase 4A, *DNMT* DNA methyltransferases 1, *HDAC2* histone deacetylase, *SAHA* Suberoylanilide hydroxamic acid, *TSA* Trichostatin A, *DTCD* 6-(4-*N,N*-dimethylaminophenyltelluro)-6-deoxy- $\beta$ -cyclodextrin, *Sp1* Specificity protein 1, *CHOP* CCAAT/enhancer-binding protein homologous protein, *15d-PGJ<sub>2</sub>* 15-deoxy-Delta 12, 14-prostaglandin J<sub>2</sub>, *NF- $\kappa$ B* Nuclear factor- $\kappa$ B, *RKIP* Raf kinase inhibitor protein, *YY1* Yin Yang 1, *HuR* Human antigen R, *Cbl* casitas B-lineage lymphoma, *USP14* Ubiquitin-specific protease 14, *UCHL5* Ubiquitin c-terminal hydrolase L5, *GALNT14* *N*-acetyl-galactosamine transferase, *GlcNAc* *N*-acetylglucosamine, *DISC* death-inducing signaling complex

or LC3, DR5 expression on cell surface is increased, leading to induction of TRAIL-induced apoptosis. However, inhibitor of lysosomal activity had no effect on DR5 surface expression (Di et al. 2013). Recently, although it is not related with TRAIL-induced apoptosis, HBx induces DR5 protein degradation via activation of autophagy. The underlying mechanisms are that DR5 is recruited to phagophores by direct interaction with HBx and autophagy induction by HBx (Shin et al. 2016). It is certain that DR5 is controlled by autophagy-lysosome pathway, but it need further study to identify the accurate mechanism. We summarized the regulation of cell death by modulation of DR5 localization (Fig. 2).

### Nucleus

DR5 has two nuclear localization signals (NLS), and nuclear localization of DR5 is correlated with TRAIL resistance. Kojima et al. reported that HeLa and HepG2 cells highly express DR5 at nucleus, and both cells are resistant to TRAIL-mediated apoptosis. In contrast, levels of DR5 nuclear expression are low in DU145 cells, which are sensitive to TRAIL. Nuclear translocation of DR5 is mediated by importin  $\beta$ 1 via the recognition of NLS sequences, and knock-down importin  $\beta$ 1 abrogates DR5 expression at the nucleus (Kojima et al. 2011).



**Fig. 2** Schematic illustration of the effect of DR5 localization on cell death. Localization and clustering in the lipid raft by modulation of autophagy and endocytosis is important on DRs-mediated apoptosis. Blue indicates modulators of DR5 localization as mentioned in our manuscript

## Conclusion

Because of TRAIL induces apoptosis preferentially in cancer cells, target for DRs-mediated signaling is promising anti-cancer strategy. For this reason, various approaches have been conducted to strengthen DRs-mediated apoptosis signals. Here, we describe the modulatory mechanisms of DR5 activation and expression (Fig. 1), and importance of DR5 localization in the cells (Fig. 2). Understanding of these mechanisms could contribute to the improvement of the anti-cancer effect using recombinant TRAIL or antagonistic monoclonal antibodies, as well as DR-specific TRAIL variant and combination treatment.

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## Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interest.

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