MINI-REVIEW

Prostate cancer: Leading and misleading routes to TRAIL of death

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Abstract: Prostate cancer is a multifaceted disease that arises because of misrepresentation of linear and integrated signaling cascades that regulate gene network in normal and cancer cells. Programmed cell death is modulated by intracellular regulators within each cell and various lines of evidence suggest that there is under- expression and over-expression of pro-apoptotic and anti-apoptotic gene subsets respectively. Apoptosis is a response to the cellular microenvironment, and the cell microenvironment can be regulated by multiple signaling cascades at a higher organizational level by suppressing survival signals notably at genetic, epigenetic, transcriptional and post-transcriptional level. Unquestionably, drug-discovery approaches over the last decade aiming at neutralizing anti-apoptotic proteins, over-expressing pro-apoptotic proteins and enhancing the cell surface appearance of TRAIL receptors have revolutionized our current information about inducing and maximizing TRAIL mediated signaling in resistant prostate cancer phenotype. In this mini-review we outline outstanding developments in the field of prostate cancer that have played a rolein understanding the underlying mechanisms that control TRAIL mediated apoptosis in prostate cancer cells, which may be helpful in the development of cancer therapies based on the apoptotic pathway.

Keywords: TRAIL, apoptosis, targeted therapy, signaling cascades.

INTRODUCTION

The genetic basis of prostate cancer is a cornerstone of biomedical and translational research that began to unravel over decades ago. Because of high impact research, this concept has undergone substantial broadening after gaining insights into the mechanisms underlying prostate carcinogenesis and central to these mechanisms are chromosome imbalances, increased mutation rates, genetic, epigenetic alterations and other forms of genetic instabilities, many of which are relevant to the development of prostate cancer.

Earlier it was presumed that spontaneous loss of tumor cells was an important stage during carcinogenesis and little was known about the mechanisms involved in cell death. Although it was shown that cells died with a morphology that was dissimilar from necrotic cells, but it was appreciated extra- ordinarily after a review published in "British Journal of Cancer" in which significance of cell death mechanism in regulation of carcinogenesis was highlighted. Later there was a continuous addition of regulators of apoptosis that increased our understanding of positive and negative regulation of apoptosis and a major breakthrough in apoptosis biology was identification of TNF super family that consisted of proteins involved in proliferation, differentiation and apoptosis. There are various review articles which address modes and mechanisms which impair TRAIL mediated signaling cascade. Reasonable knowledge of the relationship between different cell death pathways as well as between cell death and pro-survival pathways in cancer is essential for identification of prospective convergence points between signaling cascades (Farooqi *et al*, 2011; Farooqi *et al*, 2012a;b). TRAIL belongs to a small subset of proapoptotic protein ligands in the TNF super family which also includes TNF and CD95L (FasL/APO-1L). It is worth mentioning that unlike TNF and FasL, TRAIL was appreciated for triggering apoptosis in tumor cells while leaving normal tissues intact. Results obtained from laboratory investigations indicated that in mice, administration of TRAIL was efficient at reducing mammary adenocarcinoma growth without considerable tissue toxicity. This potential of TRAIL attracted scientists to explore TRAIL mediated signaling cascades in different cancers. Cellular studies indicate that TRAIL induces apoptosis through the TRAIL-R1 (DR4) and TRAIL-R2 (DR5) and it is a well established piece of

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information that DcR1 nor DcR2 are unable to induce apoptosis either due to absence of a cytoplasmic domain (DcR1) or because of a truncated death domain (DcR2) (Schneider *et al*, 1997, Walczak *et al*, 1997, Pan *et al*, 1997). Using high-throughput technologies, we are able to understand that binding of TRAIL to TRAIL-R1(DR4) or TRAIL-R2 (DR5) induces receptor trimerization. FADD is recruited to the death domains of DRs thus acting as an adaptor molecule and via second homotypic interaction, through Effector Domains present in the N-termini of both FADD and pro-caspase-8, the caspase is recruited. TRAIL receptor mediated signaling includes activation of the cell-intrinsic pathway by caspase-8-mediated cleavage of BID. BID undergoes truncation and later, truncated Bid moves into the mitochondrion that disrupts mitochondrial membrane potential thus promoting pore formation by clustering of pro-apoptotic proteins Bax and Bak, which cause release of mitochondrial cytochrome c and SMAC/DIABLO. Released cytochrome c binds to and activates intracellular receptor proteins, such as Apaf-1 activating caspase-9 and -3 (Bodmer *et al*, 2000). The pathway is represented in the fig. Introduction of expression vectors for TRAIL in cancer cells resulted in rapid production and expression of TRAIL protein, and subsequent death of the tumor cells (Griffith *et al*, 2000). However various other proteins which have predominant role in regulation of cell proliferation, differentiation and apoptosis are often not involved in TRAIL mediated apoptosis. In line with this approach, a report suggested that treatment of PC-3 cells with TRAIL also activated c-Jun NH2-terminal kinase 1 (JNK1). However genetic, pharmacologic inhibition of JNK or transfecting cancer cells with dominant-negative mutant JNK1 had little effect on TRAIL-induced apoptosis (Yu *et al*, 2000).

Convergent and divergent mechanisms in TRAIL mediated signaling

TRAIL mediated signaling is promoted and antagonized by different subsets of proteins. This section is further subdivided into two categories to discriminate between positive and negative regulators of TRAIL mediated signaling.

Positive regulators

Proof of the concept was provided by reconstituting cells with dominant negative FADD mutant that blocked PTEN-mediated apoptosis. This finding confirmed the fact that FADD and PTEN were positive regulators of TRAIL mediated signaling (Yuan *et al*, 2002). Bik and/or Bim are positive regulators of TRAIL mediated signaling and are often under expressed. However cells treated with proteasome inhibitor bortezomib displayed remarkably enhanced levels of Bik and Bim (Nikrad *et al*, 2005). Histone deacetylase inhibitors are effective when used synergistically with TRAIL in enhancing the activation of capase-3 (Sonnemann *et al*, 2005). Scientists are testing the efficacy of synthetic and natural compounds in overcoming resistance against TRAIL in prostate cancer cells and it has been shown that Mifepristone pretreatment induced increased truncation of Bid and activation of caspases -9, -7 and -3 in LNCaP (Eid *et al*, 2002a, b). Prostate cancer cells pretreated with Methylseleninic acid displayed a release of apoptogenic cytochrome c and Smac/DIABLO proteins from the mitochondria and into the cytosol (Yamaguchi *et al*, 2005).

Negative regulators

It has been confirmed that blocking the function of NFkappaB is necessary to induce apoptosis in TRAIL resistant cells. Moreover, X-linked inhibitor of apoptosis proteins are overexpressed in prostate cancer and impair TRAIL mediated apoptosis. Cells reconstructed with Smac/DIABLO displayed considerably enhanced responsiveness of cancer cells to TRAIL (Ng *et al*, 2002). PTEN activity is necessary to stimulate the expression of TRAIL. It has been shown that inactivation of PTEN results in increased Akt activity that restricts entry of FOXO protein into nucleus through its phosphorylation (Modur *et al*, 2002). Akt is activated by PI 3-kinase that inhibits BID cleavage and consequent TRAIL mediated apoptosis (Nesterov *et al*, 2001). Bcl-2 is also a negative regulator and inhibited TRAIL-induced cytochrome c release (Rokhlin *et al*, 2001). Pharmacological silencing of Glycogen synthase kinase-3beta also enhanced TRAIL mediated apoptosis (Liao *et al*, 2003). Survivin is also a negative regulator of TRAIL mediated apoptosis and cells treated with resveratrol displayed a down-regulation of survivin expression (Fulda *et al*, 2004). There is also sufficient evidence that explains that targeted inhibition of c-FLIP (L) in PC3-TR cells reversed their phenotype from TRAIL resistant to TRAIL sensitive (Zhang *et al*, 2004). Detailed mechanistic insights provide persuasive evidence that LNCaP cells express constitutively active NF- kappaB, which is inhibited by curcumin. It was earlier reported that pretreatment with curcumin inhibited the activation of NF-kappaB and sensitized LNCaP cells to TRAIL (Deeb *et al*, 2004), (Deeb *et al*, 2003). More surprisingly, Nitric oxide is also suggested to overcome TRAIL resistance by inhibiting NF-kappaB (Huerta-Yepez *et al*, 2004). It had previously been noted that introduction of expression vector for dominant-negative mutant of IKKbeta and TRAIL induced apoptosis in prostate cancer cells (Sanlioglu *et al*, 2006). Pretreating prostate cancer cells with wortmannin, a PI-3 kinase inhibitor considerably repressed Akt phosphorylation (Seol *et al*, 2005).

TRAIL joins hands with compounds

The preliminary research findings indicated that prostate cancer subtypes were resistant to TRAIL mediated apoptosis. In the next section we discuss wide ranging compounds/drugs which were used to restore sensitivity. Comprehensive studies indicate that combinatorial

approach with Doxorubicin and TRAIL resulted in a synergistic cytotoxic effect on different human prostate cancer cell lines (Wu *et al*, 2002). Additionally it has been presented that prostate cancer TRAIL resistant phenotype can be reverted to TRAIL sensitive phenotype by doxorubicin or adenoviral delivery of full- length TRAIL (Voelkel-Johnson *et al*, 2002). Likewise, Actinomycin D and gemcitabine are also tested to be effective in synergistically re-sensitizing androgen-independent prostate cancer cells to TRAIL-mediated apoptosis (Zisman *et al*, 2001). Combinatorial approach (Curcumin and TRAIL) induced activation of caspases, truncation of Bid, and release of cytochrome c from the mitochondria . Intriguingly proteasome inhibitor bortezomib and TRAIL are reported to be effective in inducing apoptosis in androgen-dependent and androgen-independent cells (An *et al*, 2003). Similarly, co-treatment of topoisomerase I inhibitor CPT-11 and TRAIL exhibited enhanced apoptotic activity in cancer cells (Ray *et al*, 2003). PS-341, a small molecule inhibitor of the proteasome works synergistically with TRAIL in inducing apoptosis in Bax negative cancer cells however the results are not remarkable in Bak negative cancer cells (Johnson *et al*, 2003). Bisindolylmaleimide IX has been reported to be effectively inducing TRAIL mediated apoptosis in TRAIL resistant cancer cells (Rokhlin *et al*, 2003). Compelling evidence suggests that translational inhibitors are potential molecules in inducing TRAIL mediated apoptosis by activating c-Jun N-terminal kinase (Sah *et al*, 2003). Na(+)/H(+) exchanger inhibitor, amiloride, has also been tested to promote TRAIL-induced cell death by promoting Akt dephosphorylation (Cho *et al*, 2005). It is of particular interest that microenvironemt is an important aspect and it is now known that human bone marrow stromal cells protect prostate cancer cells from TRAIL-induced apoptosis (Nyambo *et al*, 2004). Chemotherapeutic drugs like doxorubicin has been reported to suppress negative regulators (c-FLIP) of TRAIL mediated signaling (Kelly *et al*, 2002). Previous research methodologies gave evidence that soluble RANK-Fc (sRANK-Fc) did not block TRAIL- mediated apoptosis of LNCaP cells (Zhang *et al*, 2003).

Resistance to TRAIL mediated apoptosis can be overcome by upregulating cell surface appearance of DRs

Mechanistically it seems intriguing to note the cancer cells which are resistant to TRAIL either have under-expressed Death receptors or over-expressed Decoy receptors. Therefore surprisingly it was found that compounds that re-sensitized cells to TRAIL actually enhanced the expression of death receptors. In the forth coming section we address a list of compounds which restore apoptosis through this mechanism. Sulindac sulfide specifically up-regulated DR5 levels and pretreatment with paclitaxel resulted in elevated DR4 and DR5 protein levels (Huang *et al*, 2001), (Nimmanapalli *et al*, 2001). More significantly, topoisomerase I inhibitor topotecan increases the sensitivity of prostate tumor cells to TRAIL induced apoptosis by upregulating the DR4 and DR5 expression (Griffith *et al*, 2003). It has been investigated that treatment with indole-3-carbinol induced DR4 and DR5 expression at both transcriptional and translational levels (Jeon *et al*, 2003). Likewise, cells treated with histone deacetylase inhibitor, depsipeptide also displayed increased surface appearance of DR4 and DR5 (Vanoosten *et al*, 2005). Cells pretreated with Tunicamycin displayed up-regulated DR5 expression both at mRNA and protein levels in a dose-dependent manner (Shiraishi *et al*, 2005). Treating prostate cancer cells with synthetic retinoid, resulted in an activation of NF-kappaB alongwith an upregulation of DR4 expression and consequent apoptosis in DU145 cells (Jin *et al*, 2005). Luteolin, a naturally occurring flavonoid markedly upregulated DR5 (Horinaka *et al*, 2005). Proteasome inhibitors induced the expression of DR5 via CHOP which were noted to bind to DR5 promoter (Yoshida *et al*, 2005). The relationship of inhibitors and CHOP was confirmed by the fact that CHOP deficient cells did not respond to inhibitors mediated upregulation of DR5. It has previously been established that 5 Gy of X irradiation significantly up-regulated the expression of death receptors Fas and DR5 on the plasma membrane in prostate cancer cells (Hamasu *et al*, 2005). Pretreatment of cells with irradiation followed by TRAIL appreciably improved apoptosis by upregulating DR5 (Shankar *et al*, 2004). Furthermore, laboratory methodologies substantiate the fact that different herbal extracts are effective in inducing apoptosis in TRAIL resistant prostate cancer cells either by enforcing the expression of death receptors, targeting of anti-apoptotic proteins or restoring pro-apoptotic proteins. In accordance with this approach, ever increasing list of phytonutrients has been tested for their efficacy and minimal off target effects. Artepillin C is a bioactive component of Brazilian green propolis and has lately been shown to induce apoptosis in TRAIL resistant prostate cancer cells both by activating extrinsic (receptor-mediated) and intrinsic (mitochondrial) apoptotic pathways. There was an increase in the expression of DR5 Szliszka *et al*, 2013. Furthermore, there are some other compounds which have been shown to stimulate the expression of DR5 by rescuing p53 and directing its nuclear accumulation Xiaowen and Yi, 2013. Nortrachelogenin (NTG) is a lignan polyphenol and is a strong inhibitor of Akt pathway. It is also notable that Nortrachelogenin treated prostate cancer cells did not show growth factor mediated signaling Peuhu *et al*, 2013. Apigenin and genistein are flavonoids however apigenin has been shown to inhibit adenine nucleotide translocase-2 (ANT2) thus overcoming resistance against TRAIL in prostate cancer cells. Apigenin induced the expression of DR5 in prostate cancer cells however targeted inhibition of ANT2 in cancer cells prior to treatment with apigenin severely impaired upregulation of DR5 Oishi *et al*, 2013.

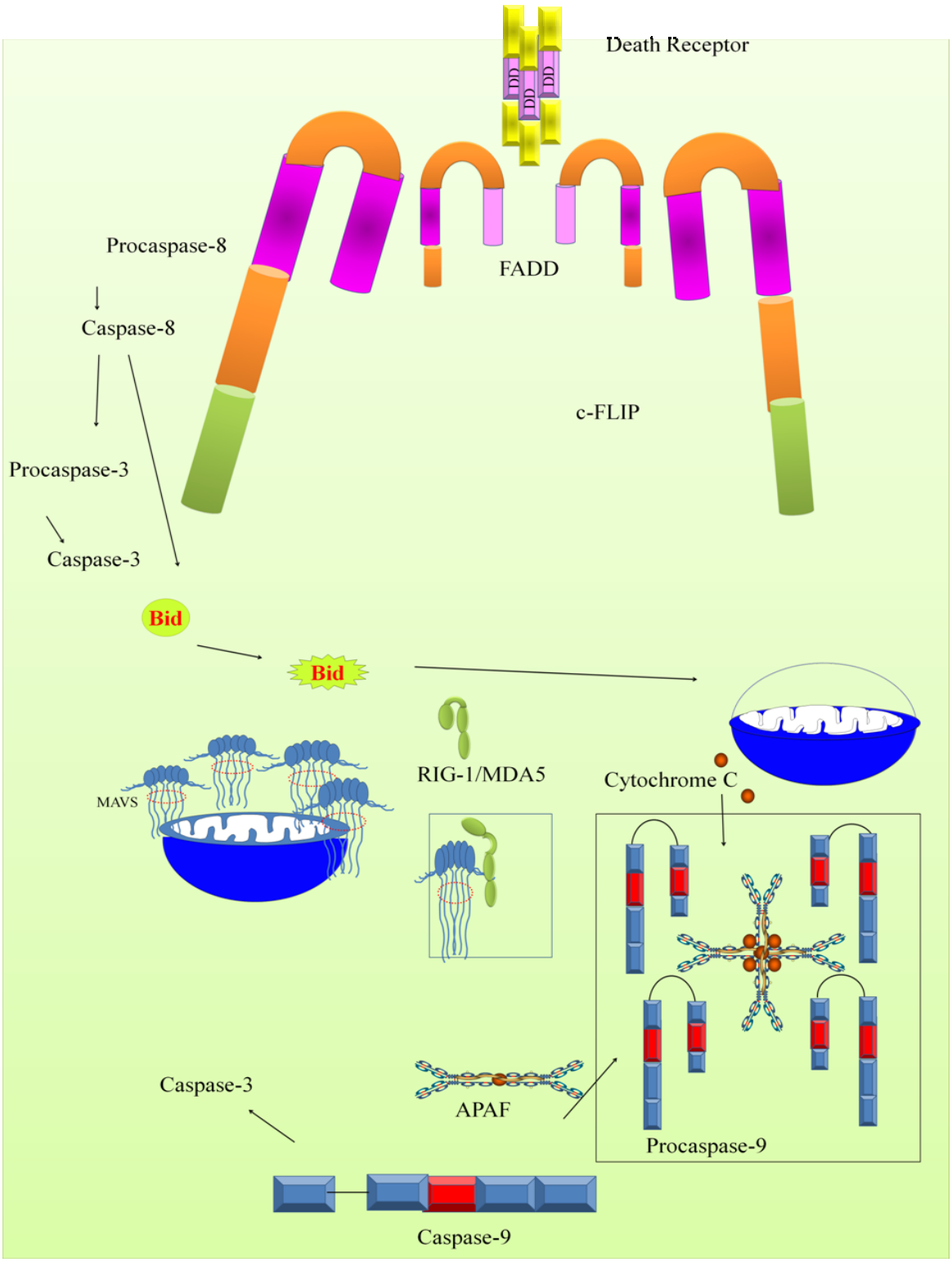

Fig shows TRAIL mediated signaling in prostate cancer cells.

Replication-incompetent Sendai virus particles have been tested for anticancer potential and evidence suggested that apoptosis was induced through RIG-I/ MAVS signaling. Gene silencing strategies verified that targeted inhibition of RIG-I/ MAVS abrogated viral particle induced apoptosis. Moreover there was a substantial increase in the expression of TRAIL and Noxa Matsushima-Miyagi *et al*, 2012. TRAIL mediated signaling is also involved in inducing autophagy and it signals through MAPK8 as the target pathway for TRAIL-induced autophagy. RNA

interference strategies confirmed that gene silencing of MAPK8 efficiently inhibited degradation of BCL2L1/Bcl-xL. Moreover MAPK deficient cells displayed marked decrease in the autophagy-suppressing BCL2L1-BECN1 complex (He *et al*, 2012).

CONCLUSION

The rapidly increasing information regarding the mechanisms that regulate cell death pathways in a positive or negative manner has offered new horizons to cancer biologists to target these pathways as an anti-cancer strategy. Despite the fact that recapitulation of cell death pathways is challenging, recent studies exploring the cell death machinery have identified various approaches especially multi-pronged approach to circumvent TRAIL mediated resistance and also novel compounds inducing cancer cell death Farooqi *et al*, 2012a; Farooqi *et al*, 2012b. It is apparent that despite tremendous advancement in our current understanding about positive and negative regulators of TRAIL mediated signaling, there are some outstanding questions which need to be experimentally verified. These questions include post-transcriptional regulation of TRAIL and its receptors. Moreover, we still do not have a complete knowledge regarding internalization and degradation of death receptors that is a major mechanism of loss of TRAIL sensitivity in prostate cancer cells. In line with this concept, there is recent evidence that gives a clue that targeted inhibition of Cbl resulted in escape of death receptors from degradation Kim *et al*, 2013. But we need to have a fuller understanding of TRAIL mediated signaling cascades encompassing post-transcriptional regulation of TRAIL, death receptors, proapoptotic and anti-apoptotic proteins. Moreover, translation of rapidly accumulating information obtained through preclinical trials of newly identified potential anticancer natural and synthetic compounds to the “bedside” is required to replace unavoidable use of chemotherapeutic drugs.

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