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Redox signaling and oxidative stress: Cross talk with TNF-related apoptosis inducing ligand activity

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ABSTRACT

Redox regulation plays a key role in several physiopathological contexts and free radicals, from nitric oxide and superoxide anion up to other forms of reactive oxygen species (ROS), have been demonstrated to be involved in different biological and regulatory processes. The data reported in the current literature describe a link between ROS, inflammation and programmed cell death that is attracting interest as new pathways to be explored and targeted for therapeutic purposes. In this light, there is also growing attention to the involvement of this link in the activity of the TNF-related apoptosis inducing ligand (TRAIL). TRAIL is a member of the TNF ligands super family able to mediate multiple intracellular signals, with the potential to lead to a range of biological effects in different cell types. In particular, the hallmark of TRAIL is the ability to induce selective apoptosis in transformed cells leaving normal cells almost unaffected and this feature has already opened the door to several clinical studies for cancer treatment. Moreover, TRAIL plays a role in several physiological and pathological processes of both innate and adaptive immune systems and of the cardiovascular context, with a strong clinical potential. Nonetheless, several issues still need to be clarified about the signaling mediated by TRAIL to gain deeper insight into its therapeutic potential. In this light, the aim of this review is to summarize the main preclinical evidences about the interplay between TRAIL and redox signaling, with particular emphasis to the implications in vascular physiopathology and cancer.

1. Introduction

The "redox signaling" is a complex regulatory process in which the signal is delivered through redox chemistry in order to generate protective responses against oxidative damage and restore the correct redox-balance between reactive oxygen species (ROS) production and their clearance by anti-oxidative/scavenging mechanisms (Droge, 2002). In this light, the original definition of oxidative stress refers to an unbalanced condition, resulting from excessive production of ROS and reactive nitrogen species (RNS) that antioxidant defense systems are not able to counteract, leading to accumulation of reactive species that play a role in several pathological contexts including inflammation, cardiovascular pathologies, atherosclerosis, metabolic alterations and cancer (Montezano and Touyz, 2012a; Panieri and Santoro, 2016). Nonetheless, the concept of oxidative stress is far more complex and its delineation has improved in the recent times with the aim of including the role of redox signaling and reactive species/molecular redox mediators, defining a research field connecting multiple disciplines including chemistry, cell biology and physiopathology (Sies, 2015). This new declination of the concept of oxidative stress accounts for the increasing evidences of the involvement of reactive species in key regulatory networks of physiological functions such as regulation of vascular tone, insulin synthesis, activation of hypoxia-inducible factor, cell proliferation, differentiation and migration (Weidinger and Kozlov, 2015), suggesting that redox biology might underlie and include both physiological and pathological contexts (Schieber and Chandel, 2014). In the absence of a widely accepted system for classification of oxidative stress, a "intensity-based" classification has been proposed, highlighting the role of the dose/concentration of the "stress-inducer" in relation to molecular/biological endpoint parameters evaluated that reflect the modifications induced by ROS (Sies, 2015; Lushchak, 2014).

In this context, the endothelium represents a biological *milieu* that in normal conditions maintains its integrity and functionality through a tight balance between opposite signals and

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pathways including anti/pro-oxidative, anti/pro-vasodilators, anti/pro-inflammatory, anti/pro-thrombotic, anti/pro-proliferative signaling (Vanhoutte et al., 2009). In the recent years, several *in vitro* and *in vivo* reports have demonstrated that the tumor necrosis factor-related apoptosis inducing ligand (TRAIL) plays an important role in vascular physiology by triggering different pathways, with a protective effect on the vascular walls and on endothelial barrier function. However, conflicting results emerge since TRAIL is a molecule able to activate pro-apoptotic/pro-inflammatory pathways but also pro-survival and anti-inflammatory cell signals. This duality is a hallmark of the TRAIL activity and the data reported about the role of TRAIL on atherogenesis represent a paradigm of this feature (Cheng et al., 2014). In fact, while a possible protective effect of TRAIL has emerged from preclinical and clinical studies (Di Bartolo et al., 2011; Secchiero and Zauli, 2012), high TRAIL levels might result in a detrimental effect on vascular integrity leading to a pro-atherogenic condition, perhaps by enhancing leukocytes adhesion and local inflammatory processes in a pathogenic loop supporting plaques formation (Michowitz et al., 2005), leaving still partially unclear the mechanisms underlying these effects. On the contrary, in the context of cancer, recombinant soluble TRAIL already represents an appealing therapeutic option that is under evaluation at the clinical level for the treatment of different types of tumor (Stuckey and Shah, 2013; Gasparini et al., 2013; Lemke et al., 2014). However, even though encouraging results are coming from the assessment of its therapeutic potential, several issues still need to be addressed such as the need to enhance TRAIL antitumor activity in order to overcome the heterogeneous sensitivity of tumors and to restore the cell sensitivity to TRAIL in the presence of TRAIL-resistance mechanisms.

Intracellular reactive species and components of the redox signaling could be critical in regulating the response to TRAIL in different physiopathological contexts. In this light, it is of interest that ROS can influence induction of apoptosis mediated by CD95 and TRAIL by affecting expression and distribution of cell receptors, making the connection between redox signaling and death receptors an important mechanism of cell regulation with significant implications. In this context, in order to shed light on the interplay between TRAIL and oxidative pathway, we set out this review to summarize the main preclinical evidences of this interaction focusing on two of the main physiopathological contexts of the TRAIL activity: the vascular/endothelial compartment and the tumor setting. Moreover, we will review and discuss the key suggestions coming from the assessment of the cross talk between TRAIL and redox signaling in order to understand the "TRAIL biology" in terms of molecular mechanisms of action and strategies to exploit the potential of TRAIL as therapeutic molecule.

2. Overview on TRAIL signaling and biology

TRAIL is a member of the TNF ligand super family that can be described as a pleiotropic molecule able to mediate multiple intracellular signals with the potential to lead to different (quite often contradictory) biological effects. This feature of TRAIL clearly emerges from both preclinical results and clinical studies highlighting the "dual-role" of this protein in several pathological conditions, spanning from immunological/cardiovascular disorders to cancer. Discovered independently by two groups more than 20 years ago (Wiley et al., 1995; Pitti et al., 1996), several subsequent *in vitro* and *in vivo* functional studies showed that TRAIL (also referred as Apo2, CD253 and TNFSF10) was able to trigger cell apoptosis in tumor cells or infected/transformed cells while leaving substantially unaffected normal cells (Ashkenazi et al., 1999; Walczak et al., 1999). Although this concept of selective pro-apoptotic activity has been revised during time as it has been reported that also some normal cells can be affected by TRAIL (Vanhoutte et al., 2009; Ursini-Siegel et al., 2002; Nesterov et al., 2002; Hayakawa et al., 2004; Janssen et al., 2005; Zauli et al., 2009). TRAIL is expressed in a wide range of tissues in both healthy and disease conditions and, in common with other members of the TNF family, can be detected as trans-membrane type protein and as soluble protein (Liabakk et al., 2002). Once expressed, the protein can be cleaved and act as soluble molecule through the generation of circulating trimers that represent the biologically active form of TRAIL *via* interaction with a system of five receptors which can be bound with different affinities (Orlinick and Chao, 1998; Yerbes et al., 2011). In particular, the TRAIL-receptor system comprises: two transmembrane pro-apoptotic death receptors (DRs) named TRAIL-R1 (DR4) and TRAIL-R2 (DR5) displaying full-length intracellular death domain, two transmembrane decoy receptors named TRAIL-R3 (DcR1) and TRAIL-R4 (DcR2) lacking an intact death domain and the soluble decoy receptor osteoprotegerin (OPG) lacking both transmembrane and cytoplasmic domains (Orlinick and Chao, 1998; Yerbes et al., 2011; Falschlehner et al., 2009). It is of interest that mRNA of all transmembrane receptors can be detected in virtually all tissues, while cell surface TRAIL protein expression is more cell-dependent. As mentioned before, the most intriguing feature of TRAIL is its ability to induce apoptosis mainly in cancer and in transformed/infected cells by interacting with DR4 and DR5. The TRAIL-mediated apoptosis pathways have been already reviewed in details (Falschlehner et al., 2007), briefly after binding to DRs, induction of apoptosis requires the assembly of a death-inducing signaling complex (DISC) at membrane level characterized by the clustering and oligomerization of intracellular death domains with the recruitment of the Fas-Associated Death Domain (FADD) and caspases-8 and -10 that are recruited and undergo autocatalytic processing followed by caspases cascade activation (Sessler et al., 2013) (Fig. 1A). In addition to caspases-mediated extrinsic apoptotic process, there is also an intrinsic apoptotic signaling triggered by the cleavage of the BH3-only protein to truncated Bid (tBid) that mediates the activation of Bax and Bak at the mitochondrial level with release of Cytochrome-C and pro-apoptotic proteins (Falschlehner et al., 2007; Sessler et al., 2013) (Fig. 1A).

Activation of TRAIL death receptors may also trigger non-apoptotic and pro-survival/proliferation signals such as those mediated by the mitogen-activated protein kinases (MAPKs), PI3K/Akt and ERK pathways and by the transcription factor nuclear factor-κB (NF-κB), all involved in the regulation of developmental and inflammatory processes (Di Pietro and Zauli, 2004; Zauli et al., 2005) (Fig. 1A). Finally, as well as other pro-apoptotic signals, TRAIL can also lead to necroptosis, a regulated and programmed form of necrosis put in place as response to severe stress and in the presence of blocked normal apoptosis (Jouan-Lanhouet et al., 2012; Chen et al., 2016). A comparison between apoptotic and necroptotic processes has been recently addressed and reviewed, highlighting the role of the different necroptotic regulators and pathways (Chen et al., 2016; Fuchs and Steller, 2015). In particular, the formation of the necroptotic-complex following stimulation is mediated by specific kinases (RIPK1 and RIPK3), that are in turn involved in the phosphorylation of the mixed lineage kinase domain like protein (MLKL), triggering the induction of downstream processes leading to cell death such as alteration of osmotic pressure and plasma membrane rupture (Fig. 1A). It has been suggested that Caspase-8 might be one of the key factors in mediating the execution of either apoptosis or necrosis. Caspase-8 is able to block necroptosis by cleaving RIPK1 and RIPK3 in favor of the apoptotic process while in the presence of Caspase-8 inhibitors and/or compromised Caspase-8 activity there is an inhibition of apoptosis in favor of the necroptotic signaling. Although the mechanisms down-streaming MLKL during necroptosis still remain to be clarified, it becomes

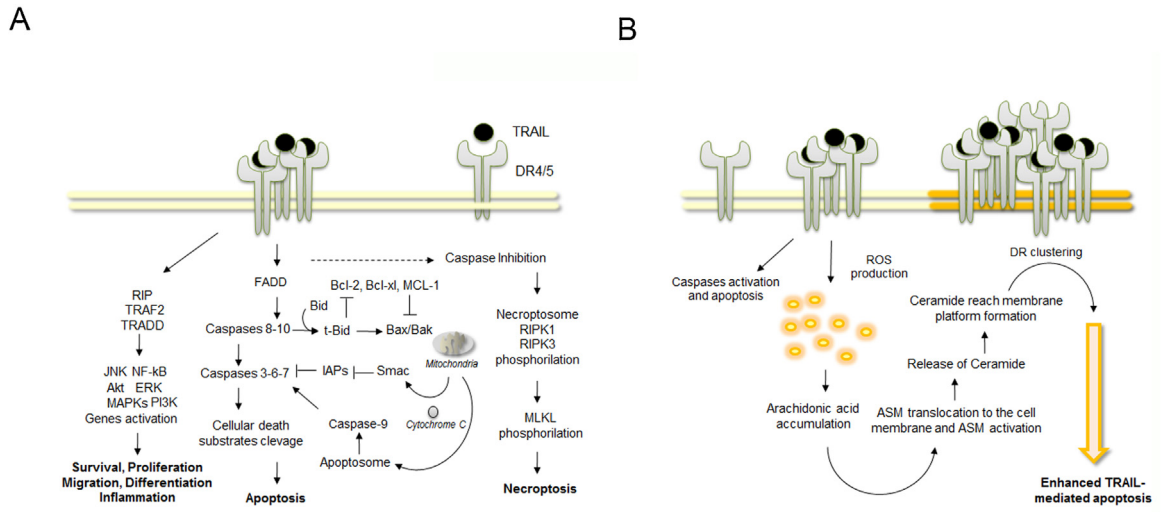

Fig. 1. Schematic representation of TRAIL-mediated apoptotic, pro-survival and necroptotic signaling. After binding to its receptors, TRAIL can initiate cell apoptosis, necroptosis or lead to cell survival. In A, the main molecular mediators involved in TRAIL-mediated pathways leading to cell survival (*via* NF-κB and kinases activation), apoptosis (*via* caspases activation) and necroptosis (*via* RIPK1-3 and MLKL) are shown. In B, a model of aggregation of TRAIL receptors in lipid rafts leading to enhanced TRAIL-induced apoptosis through the mediation of ROS and ASM production is shown. ROS are reactive oxygen species; ASM is acid sphingomyelinase; DR are death receptors.

clear that the possibility of promoting necroptosis in cancer cells represents an attractive therapeutic strategy with a strong clinical potential that deserve more investigations, in particular in light of the evidence that resistance to apoptosis is one of most challenging hallmarks of cancer.

TRAIL plays a critical role in modulating the immune system and this feature has been extensively explored in the context of diabetes mellitus (DM) (Bossi et al., 2015). In particular, both preclinical and clinical reports on Type-1 DM suggest a protective effect of TRAIL, probably through the regulation of central and peripheral tolerance carried out through a modulation of T-cells activity achieved inducing T cell apoptosis and expansion of regulatory T cells (Zauli et al., 2010; Bernardi et al., 2012a; Tornese et al., 2014, 2015). In the same fashion, TRAIL can control Type-2 DM by contrasting fat mass increase and inducing anti-inflammatory effects (Bernardi et al., 2012b; Bisgin et al., 2012; Xiang et al., 2014). The evidence that patients affected by several diseases show altered circulating TRAIL levels highlights the involvement of TRAIL in the onset/progression of the diseases suggesting a clinical potential of this molecule as a disease biomarker or as therapeutic option. Our group has significantly contributed to the demonstration of an inverse correlation between circulating TRAIL levels and pathological conditions characterized by chronic inflammation. Low TRAIL levels are associated with total and cardiovascular mortality in older adults (Volpato et al., 2011), and with poor outcome in patients affected by other pathological conditions such as myocardial infarction, coronary syndrome, heart failure and chronic diseases (Secchiero et al., 2009, 2010a; Niessner et al., 2009; Liabeuf et al., 2010; Osmancik et al., 2013; Brombo et al., 2013). Overall, these studies have suggested that TRAIL might have a role in vascular protection and control of inflammation (Secchiero et al., 2013). As regard to the regulatory mechanisms of TRAIL expression, a role has been identified for 17β-estradiol that could be involved down regulating the circulating levels of TRAIL (Zauli et al., 2014). Other hypotheses for the low TRAIL levels detected in several pathological settings, in particular in the context of cardiovascular diseases, might be due to the simultaneous increase of circulating OPG and/or to alterations of other biological parameters such as the balance between metalloproteinase-2 and tissue inhibitor of metalloprotease-2 that has been proposed to be involved in the clearance of circulating TRAIL (Secchiero et al., 2010b). Nevertheless, as previously mentioned for atherosclerosis, conflicting results have been reported on the role of TRAIL also for rheumatoid arthritis (Audo et al., 2013), allergic asthma (Tisato et al., 2014; Collison et al., 2014) and inflammatory disorders of the CNS likely as the result of different involvement/effects of TRAIL pathways in local and peripheral inflammatory processes (Tisato et al., 2016). Overall, the emerging picture describes TRAIL as a molecule able to trigger a multifaceted system of biological effects and functions, as result of a complex ligand receptors' system and of multiple levels of signal modulation/control that are put in place according to the specific cell type and to the specific biological/pathological contexts. In this line, current data suggest that DRs are definitely more than simply receptors involved in triggering an apoptotic signal, since their activation can lead to a wide panel of cellular responses. The ability of DRs to mediate conflicting cell signals might be also the result of the redistribution of DRs themselves at the cell membrane surface of target cells, with important biological and therapeutic implications. The distribution of the different receptors could account for the selective activity of TRAIL, which might be controlled by the temporal and local redistribution of its receptors. In fact, the functionality of ligand receptors, such as those for TRAIL, involves their physical association at the membrane level through the generation of membrane domains defined "rafts". These membrane domains play a key role in the transduction of the extracellular signals inside the target cell and have a strong potential as a target for new strategies to control cell death and overcome TRAIL-resistance (Delmas et al., 2004).

2.1. TRAIL and redox pathways interplay: role in vascular cells biology

2.1.1. TRAIL/TRAIL-receptors and endothelium

The selective mechanisms mediated by TRAIL leading to apoptosis almost exclusively of cancer cells and to activation of non-apoptotic pathways are still unclear (Baker and Reddy, 1996; Zhang et al., 2000; Pritzker et al., 2004; Ashkenazi and Herbst, 2008). In this line, the ongoing literature clearly documents that also in the context of vascular physiopathology the role of TRAIL remains controversial, with an overall message coherent with the "dual-face" nature of this protein. TRAIL is expressed in vascular smooth muscle cells (Gochuico et al., 2000), and although the expression of TRAIL protein at the endothelial level is still a contentious issue (Vaccarezza et al., 2007; O'Brien et al., 2007), the

presence of all TRAIL receptors in these cells is able to mediate a broad range of reactions upon stimulation by TRAIL, including inflammation, apoptosis, cell proliferation and differentiation (Zauli and Secchiero, 2006; Cantarella et al., 2014). On the other hand, the clinical evidence that circulating TRAIL levels correlate with several pathological conditions with a vascular component supports the involvement of TRAIL in the onset/progression of these diseases, with different visions about its role (Tisato et al., 2013; Harper et al., 2016; Forde et al., 2016). In this context, our group has contributed to the demonstration that TRAIL is able to promote survival and proliferation of primary human endothelial cells (Zauli et al., 2009; Secchiero et al., 2003). In particular, the pro-survival signals are mediated by phosphorylation of the serine/threonine kinase Akt *via* PI3K activation and by the stimulation of ERK1/2 pathway (Secchiero et al., 2003). In fact, in different *in vitro* studies, the inhibition of phosphatidylinositol 3-kinase (PI3K) was able to reduce P-Akt, with a concomitant reduction of Bcl-2 leading to the sensitization of the endothelium to TRAIL-mediated apoptosis *via* extrinsic and intrinsic pathways (Secchiero et al., 2003; Alladina et al., 2005). Moreover, we have also demonstrated that TRAIL down modulates the interaction/adhesion between leukocytes and endothelial cells, counteracting the pro-adhesive activity of both TNF-α and IL-1β by selectively down-regulating CCL8 and CXCL10 chemokines, with both TRAIL-R1 and TRAIL-R2 playing a role in the TRAIL-mediated effects (Secchiero et al., 2005).

2.1.2. TRAIL and ROS in endothelium

Impaired/inefficient activity of antioxidant systems such as endothelial-derived vasodilators may leads to ROS accumulation, cell damage and to a variety of pathological lesions (Sies, 1997; Cai and Harrison, 2000). In this respect, there is a widely accepted link between oxidative stress and inflammation at the vascular level, leading to endothelial cell dysfunctions (*e.g.* compromised ability to regulate the vascular tone and altered pro-coagulant and anti-inflammatory capacities), which are features of atherosclerosis and vascular diseases (Ross, 1999; Higashi et al., 2014; Siti et al., 2015). Major sources of cellular ROS include the mitochondrial respiratory chain and enzymatic reactions mediated by enzyme systems such as xanthine oxidoreductase, nitric oxide (NO) synthase (NOS) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases. The physiological and pathological relevance of these sources is different depending on the specific disease and tissue/organ. Within the enzymes responsible for ROS production, NADPH oxidases, xanthine oxidases and (uncoupled) NOS are of particularly importance in the endothelial/vascular compartment. At vascular level, primary ROS products, mainly superoxide (O_2^-) and hydrogen peroxide (H_2O_2), are indeed involved in a broad range of cellular functions related to endothelial functions/dysfunctions and vascular functional integrity including cytoskeletal regulation, cell proliferation, differentiation, migration and apoptosis (Lassegue and Griendling, 2010; Montezano and Touyz, 2012b; Raaz et al., 2014). A key role in endothelial cell biology and cardiovascular homeostasis is played by NO, a RNS synthetized from L-Arginine and involved in the regulation of the vascular tone, and anomalies in the production/bioavailability of NO are features of endothelial dysfunctions associated to cardiovascular diseases (Zhao et al., 2015). At endothelial level NO modulates several processes, including platelet aggregation, leukocyte adhesion, vascular smooth muscle cell proliferation and angiogenesis (Moncada et al., 1991; Dimmeler and Zeiher, 1999; Dimmeler et al., 1999; Fisslthaler et al., 2000; Vasa et al., 2000; Weiland et al., 2000). In this respect, our group has demonstrated that TRAIL is able to induce the production of NO upregulating endothelial NOS (eNOS, the most important enzymatic source of NO in vascular endothelial cells), by activating of the Akt/eNOS pathway and increasing the production of prostanoids *via* cyclooxygenase-1, conferring to the cells a proangiogenic and anti-inflammatory phenotype (Zauli et al., 2003). However, at the same time, in *in vitro* endothelial cell systems other groups showed that TRAIL was also able to trigger FADD-caspase-8-dependent apoptosis together with the induction of inflammatory pathways including NF-κB activation and E-selectin, ICAM-1, and IL-8 expression (Li et al., 2003). In the same fashion, in their work Pritzker and colleagues demonstrated that TRAIL was able to induce apoptosis in human microvascular endothelial cells while its decoy receptor OPG acted as survival factor (Pritzker et al., 2004). More recently in the pathological context of Alzheimer's disease, the pro-apoptotic death receptors DR4 and DR5 were shown to mediate the induction of extrinsic apoptotic pathway with activation of both caspase-8 and caspase-9 in human microvascular cerebral endothelial cells (Fossati et al., 2012). Taken together these data overall suggest that, at the endothelial level, TRAIL might have the ability to promote opposite signaling pathways acting either as pro-apoptotic signal or as pro-survival/anti-apoptotic/anti-inflammatory stimulus, encouraging the ongoing discussion.

2.1.3. TRAIL-receptors and ROS in endothelium

The reported contrasting effects mediated by TRAIL, in both normal and pathological conditions, have been also associated to the concept of the so called "lipid rafts", more recently designed as "membrane raft" (MR). MR are dynamic cell membrane domains based on cholesterol, proteins and sphingolipids/sphingolipids-metabolites that are able to mediate several cell functions (Zhang et al., 2009). The MR constitution is strictly related to the generation of ceramide via hydrolysis of membrane sphingomyelin by acid sphingomyelinase (ASM), a key event that significantly modify both cell membrane constitution and properties through the mutual interaction between sphingolipids and between sphingolipids and cholesterol resulting in the formation of distinct membrane-area. The fusion of different small ceramide-rich membrane areas leads to the generation of more large ceramide-enriched membrane platforms that organize the local and temporal distribution/clustering of cell receptors and signaling molecules driving in this way the transmission of specific cell signals and the modulation of the associated cell-pathways amplifying receptor- and stress-mediated signaling events (Zhang et al., 2009). It is of interest that there is a specific link between ceramide-mediated MR constitution and redox signaling at the vascular level with a crucial role of ceramide in amplifying redox signaling in endothelial cells leading to endothelial dysfunction (Li et al., 2010; Jin et al., 2011). In this respect, it has been shown that ceramide-reach platforms have an impact in ROS production since they are able to recruit and activate key molecules involved in ROS production such as the NADPH oxidase family, gp91phox, p47phox, Rac GTPase (Zhang et al., 2006, 2007; Jin et al., 2008). Moreover, the formation of MR-redox signaling platforms in endothelial cells is associated with a production of ceramide, mediated by lysosomal ASM that translocate at the cell membrane level after lysosomal trafficking in response to death-receptors activation (Bao et al., 2010a,b).

In the context of TRAIL, the generation of specific lipid rafts seems to be one of the possible mechanisms of action by which this ligand is able to trigger different cellular pathways with so different cellular effects. TRAIL has been demonstrated to activate ASM via a redox mechanism resulting in release of ceramide and formation of ceramide-enriched membrane platforms that are involved in the clustering of DR5, that amplify TRAIL-DR5 signaling (Dumitru and Gulbins, 2006) (Fig. 1B). In fact, in their study Dumitru and colleagues showed that antioxidants were able to prevent ASM stimulation and the release of ceramide following TRAIL treatment, leading to abrogation of ceramide-enriched membrane platforms formation and inhibiting TRAIL-induced apoptosis (Dumitru and Gulbins, 2006). More recently, Li and colleagues addressed the interaction between TRAIL signaling and cell

membrane re-organization processes in the context of endothelial cells (Li et al., 2013). In a model of murine coronary arterial endothelial cells (CAECs), the authors showed that TRAIL was able to induce the formation of redox-MR platforms with activation of NADPH oxidase and production of O_2^-, leading to endothelial dysfunction and vasodilatation (Li et al., 2013). The proposed model highlights DR4 as the TRAIL receptor involved and responsible, upon activation, of an early-stage and acute effect through the induction of the assembly and activation of NADPH oxidase in MR clusters. In particular, the authors showed that TRAIL was able to trigger the fusion of lysosomes with the cell membrane with the formation of MR redox platforms rich in ceramide leading to impaired endothelial functions. Of interest, the results obtained in the same model but in a context of ASM-deficiency confirmed the key role of ASM in mediating the TRAIL/DR4-induced formation of the redox-MR platforms and the subsequent endothelial dysfunction. The reported cell alterations were associated to increased O_2^- levels, leading to a reduced availability of NO with deficiency on vasodilatation (Li et al., 2013).

In contrast to the cytotoxic effect of TRAIL associated with ROS production, it has been nonetheless reported that ROS might be involved in TRAIL-induced protective and anti-apoptotic effect. Di Bartolo and colleagues have recently reported the results of a study aiming at understand the mechanisms of TRAIL in inducing angiogenesis and neovascularization (Di Bartolo et al., 2015) showing that NADPH enzymes, the key factors for ROS production in vascular cells, might trigger other biological effects. In a model of angiogenesis following hind limb ischemia, the authors reported a proangiogenic effect of TRAIL as downstream regulator of FGF-2, and highlighted the link between the NADPH oxidase-4 and NO signaling. In particular, endothelial cell proliferation, migration and tubule formation upon TRAIL stimulation were dependent on H_2O_2 and eNOS-derived NO signals (Di Bartolo et al., 2015). As the authors suggest in the discussion, the different results obtained in their model compared to the findings reported by Li and others, might be due to the activation of specific NADPH oxidase isoforms. In this light, in a non-endothelial model it has been demonstrated that both DR4 and DR5 can activate NADPH oxidase-1 and trigger an apoptotic pathway *via* riboflavin kinase recruitment, following an alternative mechanism of signal transduction from the conventional DISC-mediated apoptosis (Park et al., 2012).

Several reports have indeed highlighted that NADPH oxidases activation by high glucose leads to increased ROS production with endothelial damage/dysfunction, and alteration of the integrity of the endothelium by reducing NO bioavailability (Bonnefont-Rousselot, 2002; Nakagami et al., 2005; Yu and Lyons, 2005). In this context, Liu and co-workers have recently demonstrated that recombinant TRAIL significantly attenuated endothelial cell apoptosis and oxidative stress induced by high glucose in both in *in vitro* and *in vivo* experimental models (Liu et al., 2014). In particular, TRAIL was able to suppress superoxide production in an *in vivo* model of high-glucose stress by inducing a significant increase of superoxide dismutase (SOD) activity. Moreover, the *in vitro* data showed that TRAIL reduced high-glucose mediated ROS production by suppressing NADPH oxidase activity and by increasing the expression of protective factors including SOD2 and GPx-1. Signal pathways studies finally suggested that TRAIL treatment could attenuate the damage induced by diabetes at the endothelial level through the involvement and activation of the PI3K-Akt-eNOS signaling pathways (Liu et al., 2014).

Overall, the link between TRAIL and NO through the PI3K-Akt-eNOS signaling pathways appears one of the molecular networks involved in the protective role of TRAIL as supported by different groups of investigators. Nonetheless, the interaction between TRAIL and ceramide emerges as well as a critical signaling pathway in regulating the biological effects at endothelial level. In particular, deeper insight into the cross talk between TRAIL and redox signals, in MR platform formation and in TRAIL-receptors clustering processes are needed together with a better understanding of the mechanisms of action of TRAIL in relation to the different NADPH isoforms and ROS generation pathways.

2.2. TRAIL and redox pathways interplay: role in tumor biology

2.2.1. TRAIL/TRAIL-receptors and tumors

In the field of cancer therapy, TRAIL has obtained in recent years tremendous interest due to its ability to induce apoptosis in malignant tumor cells without affecting normal cells. This feature, observed in several *in vitro* and *in vivo* model systems of both solid and hematopoietic cancers, indicates TRAIL is an ideal anti-cancer drug (Walczak et al., 1999; Holoch and Griffith, 2009; de Miguel et al., 2016). On these bases, several researchers developed pharmacologic strategies, using recombinant TRAIL or TRAIL-receptor agonists (TRAs), to exploit the potential of TRAIL in clinical anticancer applications (Lemke et al., 2014). While these therapeutic approaches are under evaluation in phase I/II clinical studies (Table 1), two major issues still limit the clinical translation of TRAIL: the evidence that some tumors are TRAIL-resistant and that cancers can develop acquired resistance to TRAIL. The mechanisms by which cancer cells escape TRAIL-induced apoptosis are several (Buneker et al., 2009; Trivedi and Mishra, 2015) and innovative approaches to overcome TRAIL resistance are currently deeply investigated. Of interest, a growing number of studies indicates that TRAIL resistant cancer cells can be re-sensitized by using several agents (natural and synthetic compounds, FDA-approved drugs) targeting specific intracellular pathways (Trivedi and Mishra, 2015; Farooqi et al., 2015). Following this recent therapeutic view, a therapeutic approach based on the combination of TRAIL plus a re-sensitizing agent is at present the best opportunity to improve the TRAIL anti-tumor activity.

2.2.2. Death receptors and inflammation in cancer

Following the concept that TRAIL exerts its activity not only by inducing cell apoptosis but also by modulating other key cellular pathways such as those involved promoting inflammation, alternative cell signaling have been considered and investigated also in the context of cancer (Trivedi and Mishra, 2015; Cullen and Martin, 2015). The engagement of TRAIL receptors (and Fas) can drive the production of pro-inflammatory cytokines and chemokines after NF-κB activation (Zauli et al., 2005; Trauzold et al., 2001; Siegmund et al., 2005; Berg et al., 2009), with important implications for several disease linked to chronic and acute inflammation and for cancer biology (Trivedi and Mishra, 2015; Chen et al., 2010). Considering that NF-κB activation and protein translation are inhibited during the apoptotic process, the non-apoptotic effects of TRAIL are more evident in apoptosis-resistant cells that can acquire metastatic/invasive potential, as shown in several tumor types such as in pancreatic ductal adenocarcinoma (Trauzold et al., 2006), cholangiocarcinoma (Ishimura et al., 2006), melanoma (Takahashi et al., 2013) and breast cancer (Wang et al., 2014). Besides, in addition to its anticancer role, TRAIL might also promote the inflammatory tumor microenvironment. In this light, a relevant paper of Berg and colleagues shows that TRAIL activates pro-inflammatory pathways in 50% of primary myeloma samples, emphasizing the evidence that TRAIL should be used in combination with anti-inflammatory drugs to reduce the pro-inflammatory effects of the molecule (Berg et al., 2009). Coherently with this suggestion, it has been demonstrated that NF-κB activation can promote the expression of interleukins (such as IL-1, IL-8 and IL-6) that exert a growth promoting effect on the tumor, even though the role of NF-κB is still controversial in some tumor types (Ben-Neriah and Karin, 2011). Cullen and colleagues reported a different role

Table 1
Clinical trials with agonistic antibodies or soluble TRAIL reported on www.clinicaltrials.gov.

Cancer	n	Combination	Phase	Status	Identifier n°
Conatumumab (*AMG 655*)					
Colon	202	Modified FOLFOX6, Bevacizumab, Placebo	I/II	C	NCT00625651
Colon	53	Panitumumab	I/II	C	NCT00630786
Colon	155	AMG 479, FOLFIRI, Placebo	II	C	NCT00813605
Colon	12	AMG 479, Ganitumab, Bevacizumab	II	A (nr)	NCT01327612
Colon, Lung, Ovarian, Pancreatic, Sarcoma	89	AMG 479	I/II	T	NCT00819169
Hodgkin's lymphoma, NHL	33	Vorinostat, Bortezomib	I	C	NCT00791011
Lung	172	Paclitaxel, Carboplatin	I/II	C	NCT00534027
Ovarian, Peritoneal, Falopian Tube	27	Birinapant	I	C	NCT01940172
Pancreatic	ND	Capecitabine, Gemcitabine, Hydrochloride, Radiation	I/II	W	NCT01017822
Pancreatic, Adenocarcinoma	138	AMG 479, Placebo	I/II	C	NCT00630552
Sarcoma	134	Placebo, Doxorubicin	I/II	C	NCT00626704
AMG 951 (*rhAPO2L/TRAIL*)					
Lung	213	Bevacizumab, Carboplatin, Paclitaxel	II	C	NCT00508625
Tigatuzumab (*CS-1008*)					
Breast	66	Abraxane	II	A (nr)	NCT01307891
Colon	19	Different variants of tigatuzumab antibody	I	C	NCT01220999
Colon	21	FOLFIRI	I	C	NCT01124630
Colon	8	Irinotecan	II	T	NCT00969033
Liver, Hepatic	172	Sorafenib	II	C	NCT01033240
Lung	109	Paclitaxel, Carboplatin, Placebo	II	C	NCT00991796
Lymphoma	40	alone	I	C	NCT00320827
Ovarian	24	Paclitaxel, Carboplatin	II	C	NCT00945191
Pancreatic	65	Gemcitabine	II	C	NCT00521404
Dulanermin					
Colon	23	Bevacizumab, FOLFOX	I	C	NCT00873756
Colon	42	FOLFIRI, Bevacizumab, Cetuximab, Irinotecan	I	C	NCT00671372
NHL	72	Rituximab	I/II	T	NCT00400764
Lexatumumab					
Sarcoma, Neuroblastoma	19	Interferon Gamma 1b	I	T	NCT00428272
Mapatumumab (*HGS-ETR1*)					
Carcinoma, Hepatocellular	23	Sorafenib	I	C	NCT00712855
Carcinoma, Hepatocellular	101	Placebo, Sorafenib	II	A (nr)	NCT01258608
Cervical	9	Cisplatin, Radiotherapy	I/II	C	NCT01088347
Lung	111	Paclitaxel, Carboplatin	II	C	NCT00583830
Multiple Myeoloma	105	Bortezomib	II	C	NCT00315757
Drozitumab (*PRO95780*)					
Chondrosarcoma	90	Alone-No combinations	II	T	NCT00543712
Colon	20	Bevacizumab, Cetuximab, FOLFIRI, Irinotecan	I	C	NCT00497497
Colon	9	Bevacizumab, FOLFOX	I	C	NCT00851136
Lung	128	Bevacizumab, Carboplatin, Paclitaxel, Placebo	II	C	NCT00480831
NHL	49	Rituximab	II	C	NCT00517049
TAS266 (*Tetravalent Nanobody*)					
Advanced Solid Tumor	6	Alone-No combinations	I	T	NCT01529307
TRAIL-R1 Mab					
Lung, Carcinoma	ND	Alone-No combinations	II	C	NCT00092924
NHL	ND	Alone-No combinations	II	C	NCT00094848

NHL: non-Hodgkin lymphoma; C: Completed, A: Active; T: terminated; W: Withdrawn; Mab: monoclonal antibody; nr: not recruiting; n: number of patients enrolled; ND: number of patients enrolled not declared.

for DR-induced chemokines, introducing the concept that cells dying by pro-apoptotic signals mediated by Fas, TNF and TRAIL are not immunologically silent and may release factors able to coordinate the removal of dying cells by phagocytes (Cullen et al., 2013). The authors reported in particular the activation of a pro-inflammatory program, uncoupled from caspases activity and cell death, that results in the secretion of an array of chemokines and cytokines triggering chemotaxis toward dying cells. Their discovery suggested a sort of "find-me" signal originating from apoptotic cells and showed for the first time the DR-induced cell death as an immunologically active process.

It becomes clear that the role of TRAIL is complex and multifaceted also in the context of cancer, and the classification of TRAIL and Fas receptors as "death receptors" appears as an oversimplification since their activation is not merely cell apoptosis induction but also cytokines/chemokines production and control of cell functions such as proliferation, migration and differentiation. To take into account this complexity is therefore mandatory during the design of new anticancer therapies based on TRAIL in combination with synergistic agents, in particular to avoid pro-tumoral side effects in the case of TRAIL-resistant tumors. Moreover, it has to be consider that recent literature has shown that the majority of intracellular mechanisms of TRAIL resistance implicates disturbance of the oxidative stress "homeostasis".

2.2.3. TRAIL and ROS in cancer

Looking for intracellular targets that might help TRAIL anticancer activity, there is growing interest in the interplay between TRAIL-mediated signaling and oxidative stress responses. The link between oxidative stress and cancer is not a recent discovery, but the crosstalk with the TRAIL pathway has a more recent origin. Previous observations about the activation of NOS pathway in parallel

	Redox Mediator	Molecular induced effects	Target	Biological effect	Ref.
Vascular	NO	Activation of the Akt/eNOS pathway	Human vein endothelial cells	Induction of proangiogenic and anti-inflammatory phenotype	Zauli et al. (2003)
	ROS (O_2^-), ASM	Redox amplification mediated by ASM	Coronary arterial endothelial cells	Activation of DR4-signaling and endothelial dysfunction	Li et al. (2013)
	NOX, H_2O_2, NO	NOX involvement with H_2O_2 and NO production	*In vivo/in vitro* model of angiogenesis	Pro-angiogenic phenotype, cell proliferation, migration and tubule formation	Di Bartolo et al. (2015)
	NO, SOD_2 GPx-1	Activation of the Akt/eNOS pathway and expression of protective factors	*In vivo* model of diabetes *In vitro* endothelial model	Suppression of high-glucose ROS production and of cell apoptosis	Liu et al. (2014)
Cancer	ROS (O_2^-), ASM	Redox amplification mediated by ASM	Cancer cells	Activation of DR5-signaling and cell apoptosis	Dumitru and Gulbins (2006)
	NO	Activation of caspases and stimulation of NO production	Haematological malignancies	Apoptosis and cell cycle abnormalities	Secchiero et al. (2001)
	ROS (O_2^-, H_2O_2) ER stress	Upregulation of DR4/DR5 Cell depolarization, ROS generation and mitochondrial apoptosis	Several types of tumors	Enhanced TRAIL-induced tumor cell death	Yamaguchi and Wang (2004), Tse et al. (2014), Li et al. (2015), Iurlaro and Munoz-Pinedo (2016), Suzuki et al. (2012), Inoue and Suzuki-Karasaki (2013), Suzuki-Karasaki et al. (2014a)
	GSR	Inhibition of GSR activity results in induction of oxidative stress and increase in ROS	Melanoma and carcinoma	Promotion of TRAIL-induced cell death	Rozanov et al. (2015)
	ONOO-	Enhanced mitochondria-mediated caspase pathway	Human colorectal carcinoma	Improved TRAIL-induced cytotoxicity	Lee et al. (2001)
	ONOO-	Increase in the localization of DR4 to the lipid raft subdomains of plasma membrane	Different sets of cell lines and their cisplatin-resistant variant	TRAIL restored sensitivity of resistant cells to cisplatin	Seah et al. (2015)
	ROS (H_2O_2)	Cisplatin-induced mild oxidative stress	Ovarian cancer cell model	Increased TRAIL-resistance	Choi et al. (2010)

Fig. 2. Redox signaling and TRAIL biological activity. The picture shows some of the molecular mediators of the cross talk between redox signaling and TRAIL biological activity. NO is nitric oxide; ROS are reactive oxygen species; ASM is acid sphingomyelinase; SOD is superoxide dismutase; ER is endoplasmic reticulum; GSR is glutathione reductase; DRs are death receptors; NOX are NADPH oxidases; O_2^- is superoxide; H_2O_2 is hydrogen peroxide; $ONOO^-$ is peroxynitrite.

to caspases cascade after TRAIL treatment were made by our group in leukemic cells (Secchiero et al., 2001) and TRAIL and ROS were investigated by other groups in different preclinical models of solid cancer. For example, it has demonstrated that ER stress/ROS (H_2O_2 and O_2^-) induction can result in the upregulation of DR5 in human carcinoma cell lines (Yamaguchi and Wang, 2004) and, associated to the downregulation of survivin, in TRAIL-resistant melanoma cells (Tse et al., 2014). Moreover, regulation of DR4 and DR5 expression has been associated to ER-mediated apoptosis in human lung cancer cells treated with ER stress inducing agents (DDIT3 and KAT2A) (Li et al., 2015). Several other reports indicate that TRAIL receptors DR4 and DR5 can be induced by ER stress, suggesting that ER stressor drugs, such as thapsigargin, can be used to sensitized cells to TRAIL-mediated apoptosis (Iurlaro and Munoz-Pinedo, 2016).

Other studies describe a different mechanism of interaction between TRAIL and redox signaling *via* cell membrane depolarization, due to impairment of ion channels or transporters of Na^+, K^+, Cl^- and Ca^{2+}, and to disruption of intracellular ion homeostasis, leading to apoptosis. Several human malignant tumor cells (including melanoma, leukemia and lung cancer), but not normal cells, show robust and persistent depolarization after TRAIL treatment in a dose and time-dependent manner and in correlation with the specific cell sensitivity to TRAIL-induced apoptosis (Suzuki et al., 2012; Inoue and Suzuki-Karasaki, 2013; Suzuki-Karasaki et al., 2014a). This type of depolarization has been described as an early and pro-apoptotic event induced also by other pro-apoptotic well defined agents such as Fas, rotenone and arsenic trioxide (Bortner et al., 2001; Nolte et al., 2004; Yin et al., 2009), and it is associated with activation of the mitochondrial apoptotic pathway and ROS generation. In this line, the results reported by Suzuki-karasaki (Suzuki-Karasaki et al., 2014a) suggest the existence of a positive loop between depolarization and mitochondrial-derived ROS (O_2^-) accumulation through DR5 expression, although the specific mechanism of modulation and the role of Na^+-K^-ATPase still need to be defined in the context of TRAIL-induced apoptosis. In this regard, a variety of compounds capable of further increase the intracellular levels of ROS induced by TRAIL, in particular H_2O_2, has been shown to have the capability to potentiate the TRAIL antitumoral efficacy in several tumor models (Suzuki-Karasaki et al., 2014a,b) and offers increasing opportunity of therapy. Of interest, also several natural pharmacological agents have shown the potential to sensitize cancer cells to TRAIL apoptotic activity *via* ROS production and the evidence that they are able to upregulate TRAIL-DRs makes them an appealing therapeutic option to be explored also at the clinical level in combination with recombinant TRAIL or DRs-agonist antibodies (Supplementary Table 1). Another key component of the oxidative stress response, the enzyme Glutathione reductase (GSR), has been shown to be involved in the TRAIL-mediated apoptosis in melanoma and carcinoma cell lines of different origin (prostate, pancreatic, lung and breast). In this setting, new compounds, identified by high throughput screening and able to inhibit the activity of GSR, with a concomitant drop of intracellular antioxidant reduced glutathione (GSH) and induction of oxidative stress, have been shown to potentiate TRAIL toxicity *in vitro* and in mouse xenograft models (Rozanov et al., 2015), offering another weapon to support TRAIL anticancer skills.

The interplay between oxidative stress and TRAIL-induced apoptosis has been also reported for specific NO-derived chemical species, referring in particular to peroxynitrite, a highly reactive free radical resulting from the rapid interaction between NO and superoxide (Stamler et al., 1992). Once generated, peroxynitrite acts as a potent oxidant able to trigger a wide range of effects culminating in cell dysfunction, apoptosis or necrosis (Virag et al., 2003) and it has been suggested to be able to potentiate TRAIL-induced apoptotic death (Lee et al., 2001). In addition, in a recent work Seah and colleagues have highlighted the role of peroxynitrite in mediating the TRAIL-mediated apoptotic effect in cisplatin-resistant cancer cells (Seah et al., 2015). In line with previous findings, the authors detected mitochondrial defects on cisplatin-resistant lung and ovarian cancer cells compared to wild type (cancer) cells and reported a higher susceptibility of these cells to TRAIL-induced apoptosis. This effect on cisplatin-resistant cells was in particular associated with a different re-destribution of DRs to lipid rafts on the plasma membrane, increased iNOS expression with subsequent NO generation by target cells highlighting the key role of peroxynitrite that appears to be required for maximal TRAIL-induced cell death. It is of interest that this study suggests the presence of a positive feedback loop with DRs activating caspases with increased

iNOS activity leading to NO release and peroxynitrite production that in turn amplify death execution (Seah et al., 2015).

Overall, there is increasing evidence suggesting that tumor cells are more suitable than normal cells to oxidative stress and depolarization and more exposed to mitochondrial network abnormalities and that this vulnerability can be relevant to the tumor-targeting killing by TRAIL. Moreover, considering that: i) cancers can originate from chronically inflamed tissues (Reuter et al., 2010); ii) inflammation is tightly regulated by the redox signaling (Lei et al., 2015) and that iii) increasing reports highlight the role of TRAIL signaling in both inflammation and redox modulation, there is growing attention to TRAIL as a key element able to talk with and modulate all these pathways. This feature, together with the pro-apoptotic anticancer capability of TRAIL, can be tailored and guided for several purposes. In particular, the synergy between TRAIL and molecules able to target one of the mentioned pathways will provide efficacious combinations able to target and kill even TRAIL-resistant tumors while saving normal cells.

3. Concluding remarks

While ROS were initially considered species responsible only for cell damage and cell death, their role has been now revised in light of their involvement in a more complex range of reactions including signal transduction pathways and regulation of several cell functions. The attempt of defining the specific type of oxidative stress in each physiopathological and/or experimental context, perhaps by using the proposed "intensity-based" classification (Lushchak, 2014), is still a challenging task since specific and strict guidelines to discriminate between different levels/ranges of oxidative stress are needed. In the context of TRAIL, there is growing interest in understanding how reactive species and redox mediators can interfere with its pathways and mechanisms of action since these knowledge might be used to improve and optimize its biological activity. The binding of TRAIL to its surface receptors is far more that simply caspases activation and the mechanisms of protection of normal cells against apoptosis as well as the ability of activate opposite pathways leading to different biological outcomes are not clear and need further insights. In this light, the concept of membrane trafficking and the demonstration of a cross talk between oxidative system and ASM pathway in DR-mediated signaling activation has shed some light on the regulation of endothelial cell functions and on TRAIL-induced effects (Fig. 2). In the context of cancer TRAIL already represents a therapeutic option under evaluation used either alone or in combination with other molecules, in particular with ROS inducers, in order to trigger TRAIL-mediated apoptosis (Fig. 2). Nonetheless, it has been recently showed that mild oxidative stress contributed to escape TRAIL-mediated apoptosis and mediated TRAIL tolerance in an ovarian cancer model (Lu et al., 2016), in agreement with previous findings about the promoting role of ROS in TRAIL resistance (Choi et al., 2010). These contradictory results, in line with the "dual" nature of TRAIL, highlight the need of further investigations to gain deeper insights on the mechanisms of TRAIL resistance and on the quantification of the real intracellular ROS concentrations in relation to the modifications induced in ROS targets in each experimental/physiopathological condition. Further investigations are also required to clarify other issues such as the mechanisms of DR recruitment and the formation of redox signaling platforms upon TRAIL stimulation and the functions/effects induced by "local doses" of the TRAIL input.

Finally, new mechanistic comprehensions of the link between ROS and redox signaling with TRAIL-induced responses in specific cell subsets in different physiopathological contexts, including cancer, will help to understand the "life-death" signaling mediated by TRAIL, with significant therapeutic implications.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.biocel.2016.09.019.

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