Impact of death receptor signaling on the malignancy of pancreatic ductal adenocarcinoma

Christian Röder, Anna Trauzold, Holger Kalthoff*

Sektion für Molekulare Onkologie, Institut für Experimentelle Tumorforschung, Krebszentrum Nord – CCC, Universitätsklinikum Schleswig-Holstein, Campus Kiel, 24105 Kiel, Arnold-Heller-Str. 3, Haus 18, Germany

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC), a type of tumor with late diagnosis, rapid progression and poor prognosis. It is mostly unresponsive to chemo- and radiation therapy due to a marked resistance against apoptosis induction via both the intrinsic and extrinsic pathway. Accordingly, also activation of death receptors of the TNF-receptor superfamily does not or hardly induces apoptosis in PDAC cells. The reasons for this resistance include expression of multiple inhibitory proteins that block apoptotic signaling at almost every step of the signaling cascade. Moreover and more importantly, death receptors such as CD95/Fas, TRAIL-R1/-R2 and TNF-R1 exhibit marked non-apoptotic functions after ligand binding leading to strong proinflammatory responses, which contribute to survival, proliferation, migration and invasion, causing an even more pronounced malignant phenotype. This non-apoptotic signal transduction is facilitated via distinct adapter proteins, such as TRAF2 that bind to death receptor complexes and stimulate proinflammatory signal pathways leading to activation of NF-κB and AP-1 transcription factors. Therapeutic interventions in oncology utilizing death ligands, e.g. TRAIL, or triggering death receptors indirectly, must be carefully evaluated with respect to possible “side effects” and should be designed in a way counteracting non-apoptotic proinflammatory signaling.

Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) holds the 4th rank in the statistics of cancer related deaths in the U.S. (Jemal et al., 2010) and is still a devastating disease with the urgent need of improved diagnostics and new therapeutic strategies. PDAC is characterized by the absence of early and specific symptoms and shows a rapid disease progression. This largely precludes early diagnosis and curative treatment. Thus, the overall 5-year-survival rate is only 1–4%. Surgical resection represents the only curative treatment option, but due to the late diagnosis, most patients present in an advanced stage and only a minority (10–20%) is amenable to surgical intervention, yielding a 5-year-survival rate of 15–25% in this subgroup [reviewed in Loos et al. (2008)]. The vast majority of patients rely on palliative treatment resulting in a median survival of just a few months. This desperate situation is due to the fact that PDAC cells adopt a malignant phenotype quite early during tumorigenesis, giving rise to a highly metastatic and chemoresistant phenotype (Farrow et al., 2008). It is now established that PDAC exhibits a sequential histological and genetic progression of precursor lesions (pancreatic intraepithelial neoplasias, PanINs) culminating in invasive neoplasia (Koorstra et al., 2008). A hallmark of PDAC is the development of an accompanying malignant inflammation resulting in invasive growth, dissemination, and stromal proliferation (desmoplasia) (Mihaljevic et al., 2010). Also for PDAC, a tumor stem cell concept has been postulated and experimentally substantiated. PDAC cells with stem cell-like behavior could be identified by functional characteristics and by specific marker expression. This stem cell model is currently the subject of intense discussion and will strongly influence aspects of tumor biology and therapeutic approaches in pancreatic cancer (Ischenko et al., 2010).

Malignant transformation of healthy cells is first characterized by uncontrolled and often rapid proliferation. Malignant cells also permanently acquire many features of cells involved in tissue repair and wound healing, such as de-differentiation, active cell division, migration and invasion that are mediated by secretion of proinflammatory, proteolytic, chemotactic and growth-promoting factors. These changes are also related to processes known as epithelial–mesenchymal transition (EMT) (Thiery et al., 2009). A complex intrinsic cascade of cellular control mechanisms is normally active to timely terminate such state of activation. The ultimate weapons of a cell against its own loss of control are pathways leading to commitment of cellular suicide. Apoptosis, which is induced either intrinsically, e.g. after administration of cytotoxic, DNA-damaging agents, or can be triggered extrinsically via
activation of death receptors, is the major form of cellular suicide. The malignancy of pancreatic ductal adenocarcinoma cells is largely based on multiple and synergistically acting resistance mechanisms against apoptotic challenge accompanied by a striking capability to shift death receptor signaling (CD95 and TRAIL-R, as well as TNF-R) towards stimulation of inflammation and invasion. The contribution of apoptosis signaling defects to PDAC malignancy was recently confirmed by a comprehensive study analyzing genetic alterations in primary PDAC specimen (Jones et al., 2008).

Dual role of death receptors in PDAC cells

Since the first description of CD95/Fas/Apo-1, this member of the TNF receptor superfamily has been regarded as paradigmatic for death receptors, capable of inducing caspase-driven apoptosis (Itoh et al., 1991). More recently, CD95 has also emerged as an inducer of other signaling pathways including those controlling inflammation and migration (Sancho-Martinez and Martin-Villalba, 2005). These non-apoptotic signal transduction mechanisms of CD95 and other members of the death receptor family became particularly obvious in apoptosis-resistant tumor cells and the many facets of this matter had been recently summarized (Kalthoff and Trauzold, 2009) and are schematically depicted in Fig. 1. One of the take-home lessons here and in the accompanying papers of an edited book (Kalthoff, 2009) clearly states that it is neither only apoptotic nor non-apoptotic signaling, but rather the balance between both that determines the final outcome of death receptor stimulation.

The synthesis of CD95 and CD95L in pancreatic tumors and PDAC cell lines was extensively studied, revealing a frequent and strong expression of these two components of an autocrine machinery (Ungefroren et al., 1998). We observed a CD95L-dependent killing of Jurkat cells by PDAC cells, while these show a frequent resistance to apoptotic challenge correlating with expression of the Fas-associated phosphatase (FAP)-1 (Ungefroren et al., 1998). The mechanistic impact of FAP1 (Yanagisawa et al., 1997) on CD95-mediated resistance in PDAC cells was elucidated using microinjection of a tripeptide inhibitor of the FAP1–CD95 interaction (Ungefroren et al., 2001). Interestingly, CD95 signaling is not involved in chemotherapeutic/gemcitabine-induced apoptosis in PDAC cells, despite gemcitabine-mediated CD95 upregulation at the cell surface (Christgen et al., 2005). It could be further demonstrated that multiple resistance mechanisms against apoptosis induction are active in PDAC cells both constitutively and after activation of the extrinsic death receptor signaling or the intrinsic pathway by challenge with chemotherapeutics (Müreköster et al., 2003; Trauzold et al., 2001, 2003a,b).

Another member of the TNF cytokine family, TNF-related apoptosis inducing ligand (TRAIL), has drawn major attention in the last years for its potential utilization in cancer therapy. It has been described to induce apoptosis in tumor cells while leaving normal cells undamaged (Armeanu et al., 2003; Ashkenazi et al., 1999; Lawrence et al., 2001; Walczak et al., 1999). More recently, this paradigm was challenged by reports observing TRAIL resistance of tumor cells (Falschlehrer et al., 2009; Trauzold et al., 2003a) and, moreover, an increase in malignant behavior of apoptosis-resistant tumor cells driven by ligand-induced non-apoptotic signaling of TRAIL receptors (Ehrenschwender et al., 2010; Siegmund et al., 2007; Trauzold et al., 2006). However, the recombinant ligand, as well as agonistic anti-TRAIL-R1/DR4 (Mapatumumab) and anti-TRAIL-R2/DR5 (Lexatumumab) antibodies are evaluated in clinical studies (phase I/II) for suitability as therapeutics against different malignancies (Duiker et al., 2006; Johnstone et al., 2008; Rownisky, 2005; Takeda et al., 2007). Interestingly, it could very recently be shown by use of different TRAIL-R-specific antibodies that TRAIL exerts its apoptotic as well as non-apoptotic signaling predominantly via TRAIL-R (Lemke et al., 2010).

Besides the apoptosis-related functions of death receptors like CD95, TRAIL-R1⁄R2 or TNF-R1, some groups demonstrated effects of these receptors not leading to or even preventing apoptosis (Kalthoff, 2009; Park et al., 2005). It was shown in various cell types including PDAC- and other tumor cells that death receptor ligands CD95L and TRAIL activate non-apoptotic signaling such as protein kinase (PK)-C and NF-κB pathways, protecting the cells from death [for review: Wajant et al., 2003]. With respect to normal, non-malignant cell types, non-apoptotic death receptor signaling was shown to induce proliferation of TCR-stimulated T-cells and thymocytes (Alderson et al., 1993) as well as the proliferation of human diploid fibroblasts (Aggarwal et al., 1995). Moreover, CD95 accelerated the liver regeneration after partial heptectomy in mice (Desbarats and Newell, 2000) and stimulated neurite growth in vitro and regeneration after nerve injury in vivo (Desbarats et al., 2003).

Apoptotic signaling in PDAC cells

TNF-R, CD95 and TRAIL-R death receptors are transmembrane proteins sharing a particular homology, since all are members of the TNF receptor superfamily. They contain a common conserved intracellular “death domain” necessary for adapter protein binding and apoptosis induction. The active receptors aggregate as trimeric molecules upon binding of the trimeric ligands. The ligated trimeric receptor/ligand complex is capable of recruiting several additional adapter proteins into a large multi-protein complex designated as death-inducing signaling complex (DISC) (Kischkel et al., 1995). Within the DISC and downstream of death receptor activation caspases play a crucial role in the signal transduction. It was shown that PDAC cells belong to the type II cells with respect to apoptosis induction (Hinz et al., 2000). They are characterized by only...
weak and delayed activation of caspase-8 at the DISC (Scaffidi et al., 1998) thus following the mitochondrial pathway of apoptosis, as was proven by the capability of BclxL to almost completely block apoptosis in PDAC cells (Hinz et al., 2000). Cell types displaying a fast and strong activation of caspase-8 and subsequent direct cleavage of caspase-3 upon death receptor activation are designated as type I cells and they are independent of the mitochondrial signaling loop (Scaffidi et al., 1998). Briefly (compare Fig. 1), mitochondrial apoptosis signaling comprises Bid cleavage initiated even by small amounts of active caspase-8, mitochondrial outer membrane destabilization leading to cytochrome C-release and apoptosome-formation, activating caspase-9. Subsequently, caspase-8 and the effector caspases-3, -6, -7 are cleaved and activated (reviewed in: Hamacher et al., 2008).

Apoptosis resistance mechanisms

One of the early known mechanisms described in pancreatic tumor cells to confer resistance against CD95-mediated apoptosis and, furthermore, to stimulate proliferation, was the expression and activity of protein kinase (PKCδ)/PKD1 (Trauzold et al., 2001, 2003b). Subsequently, several additional resistance mechanisms against CD95 or TRAIL-R apoptosis in PDAC cells were reported (Trauzold et al., 2003a). Actually, each step in the apoptotic signal cascade can be blocked by inhibitory proteins such as decoy receptors (in the case of TRAIL signaling), cFLIP isoforms, anti-apoptotic Bcl2 family members, IAP family proteins (Falschlehner et al., 2007). Among these mechanisms in PDAC cells, we also found that JNKs can play a dual role in apoptosis signaling. Although JNKs are activated during both, chemotherapeutic (gemcitabine)- and apoptosis resistance (Knippschild et al., 2005). We could demonstrate that low expression levels of Bid lead to constitutive protection of PDAC cells against apoptosis (Trauzold et al., 2005). Inhibition of CK1δ led to a decreased proliferation and sensitized cells for CD95-mediated apoptosis.

Besides JNKs, PKC (especially PKCδ/PKD1) and ERK1/ERK2, which play protective roles in death receptor mediated apoptosis of pancreatic tumor cells, we also demonstrated that a member of the stress-activated serine/threonine-specific casein kinase (CK)-1 family, CK1δ, is highly expressed in PDAC cell lines and also in pancreatic tumor tissues and is involved in the control of growth and apoptosis resistance (Brockschmidt et al., 2008). Inhibition of CK1δ led to a decreased proliferation and sensitized cells for CD95-mediated apoptosis.

One of the known phosphorylation targets of casein kinases-1 and -2 is the apoptosis regulator Bid (Knippschild et al., 2005). We could demonstrate that low expression levels of Bid lead to constitutive protection of PDAC cells against apoptosis (Trauzold et al., 2003a). The phosphorylation of Bid by CK1 and CK2 was also shown to inhibit its cleavage by caspase-8, thus blocking the formation of pro-apoptotic truncated Bid (tBid) (Desagher et al., 2001). Importantly, we could recently demonstrate that specific inhibition of constitutively active CK1δ led to an efficient Bid-cleavage, and furthermore, resulted in the down-regulation of IAP expression (Brockschmidt et al., 2008). These results underline the role of CK1δ in constitutive apoptosis resistance of PDAC cells.

A low expression level of Bid could also reflect epigenetic modifications of the bid gene, since treatment of PDAC cells with 4-phenylbutyrate (4-PB), an inhibitor of histone deacetylases, upregulates Bid-expression and sensitizes cells against chemotherapy (Ammerpohl et al., 2007). Similar results were also obtained in another study investigating SCID mice bearing orthotopic lung (NSCLC) tumors. A combination treatment with 4-PB and gemcitabine in this model revealed a substantial therapeutic efficacy and it was shown that the intrinsic apoptosis signaling as well as pro-apoptotic JNK signaling are significantly contributing to the therapeutic effect of this drug combination (Schniewind et al., 2006).

To gain further insight into the complexity of multiple resistance mechanisms and to uncover possible new regulatory aspects of signal transduction, a mathematical model for description and understanding of CD95-mediated apoptosis signaling and apoptosis resistance was developed as a novel approach and as a joint project of cell- and molecular biology laboratories and a theoretical bioinformatics group (Bentele et al., 2004). This modular model describes the regulation of apoptosis on a systems level and was established and fed using quantitative protein expression data from analyses of the human B lymphoblastoid cell line SKW 6.4, previously classified as type I cells. As an important output of this computational approach and as a novel regulatory detail of CD95 signaling a threshold behavior of cFLIP for the regulation of CD95-mediated apoptosis was predicted by the model and was subsequently confirmed as a “wet-laboratory” experiment (Bentele et al., 2004). Recently, a similar approach utilizing whole genome microarray gene expression data of micro-dissected pancreatic tumor tissue confirmed the utility of such computational analyses to model even complex pathways like apoptosis (Rückert et al., 2010). As important result in this analysis, IL1-R2 was predicted to be involved in PDAC development. This takes up earlier results showing that the interleukin-1 signaling contributes to the malignant potential of PDAC (Arlt et al., 2002; Müllerköster et al., 2004).

Non-apoptotic signaling

Analyses of the expression of DISC-interacting proteins revealed that all apoptosis-resistant PDAC cells overexpress the TRAF2 protein. Furthermore, more than 90% of clinical specimens of pancreatic tumors showed strong upregulation of TRAF2-expression (Trauzold et al., 2005). We could further demonstrate by introduction of a TRAF2 expression vector into PDAC cells that high TRAF2 expression protects cells from CD95-mediated apoptosis. It also leads to constitutive upregulation of NF-κB and AP-1 activity and, in consequence, to the overexpression of urokinase-type plasminogen activator (uPA), matrix metalloproteases (MMP)-2/-9, IL8 and it strongly enhanced invasiveness. Moreover, triggering of CD95 in TRAF2-overexpressing cells resulted in further enhanced activation of NF-κB and AP-1 followed by induction of IL8- and uPA-expression, and consequently led to an even more enhanced invasiveness (Fig. 1). Thus, TRAF2 overexpression does not only block apoptosis induction by CD95 but converts this death receptor into a mediator of invasiveness (Trauzold et al., 2005). Such motility- and invasiveness-promoting role of CD95 has also been shown in other tumor cells (Barnhart et al., 2004; Chen et al., 2010) and, very recently, in peripheral myeloid cells mediating tissue damage in inflammatory processes (Letellier et al., 2010).

Interestingly, we found that overexpression of TRAF2 strongly enhances not only non-apoptotic signaling of CD95, but also of TRAIL receptors. This underlines the role of TRAF2 as a master switch in the pathophysiology of pancreatic adenocarcinoma, predestining this protein as an excellent target for therapy. The polyphenolic compound catechin gallate, a substance naturally contained in green tea, could be identified as a TRAF2 down-regulating agent in PDAC cells (unpublished observation). Consequently, catechin gallate inhibits TRAIL-mediated activation of NF-κB and strongly enhances TRAIL-induced apoptosis in conjunction with a clear decrease in invasiveness. Interestingly, the structurally related compound epigallocatechin gallate did not show the same effect on TRAF2. With these findings catechin gallate emerged as a promising new candidate for a combination treatment of PDAC.
Investigation of death receptor-induced non-apoptotic signaling in PDAC cells revealed that both, CD95 and TRAIL-R mediate activation of PKCs, JNK, p38, ERK1/ERK2 and of the transcription factors NF-κB and AP-1 (Siegmund et al., 2007). Notably, PKC, ERK1/2 and NF-κB pathways inhibit apoptosis, and in parallel induce the expression of inflammation- and invasiveness-promoting proteins like IL-8, MCP-1, MMPs and uPA. These proteins enhance the migration and invasion of apoptosis-resistant PDAC cells in an in vitro assay (Trauzold et al., 2005). Most importantly, it could also be demonstrated that intraperitoneal administration of TRAIL in SCID mice bearing orthotopic pancreatic tumors results in strikingly increased liver metastasis and peritoneal carcinoma metatosis (Trauzold et al., 2006). Thus, besides apoptosis induction, TRAIL is able to stimulate the entire complex metastatic cascade of solid tumor progression under in vivo conditions. Other reports showed promotion of migration and invasion by TRAIL in vitro for apoptosis-resistant cholangio- and colorectal carcinoma cells. This was explained as a consequence of the activation of NF-κB (Ishimura et al., 2006) or a K-Ras-/F1-dependent pathway, respectively (Hoogwater et al., 2010). Moreover, pro-inflammatory, growth stimulating, as well as pro-angiogenic activities of TRAIL were demonstrated (Begue et al., 2006; Li et al., 2003; Morel et al., 2005; Secchiero et al., 2004).

Besides TRAIL and CD95L also TNFs is a well known inducer of inflammatory responses in tumor cells as well as in non-malignant situations. Therapeutic substances blocking TNF have been proven beneficial in the treatment of chronic inflammatory diseases like psoriasis, rheumatoid arthritis, Crohn’s disease or ulcerative colitis. Meanwhile, over 105 patients have been treated worldwide with recombinant soluble TNF receptors or anti-TNF antibodies (Van Herreweghe et al., 2010). These TNFα antagonists (etanercept and infliximab) were also used in a recent therapy study utilizing an orthotopic SCID mouse model for pancreatic carcinoma. Here, it was demonstrated that pancreatic tumor cells secrete TNFs, which can induce the pro-inflammatory non-apoptotic signaling cascade (Ebghertz et al., 2008a). This model comprises a clinically adapted surgical resection scheme where the experimental primary tumor is surgically removed, in order to investigate a possible subsequent relapse (Tepel et al., 2006). This study also revealed that tumor cell-derived TNF is responsible for recurrent tumor growth and metastasis after removal of the primary tumor. Importantly, administration of the anti-inflammatory drug dexamethasone was able to significantly reduce recurrent disease in this model (Ebghertz et al., 2008b).

Also for non-apoptotic signaling the relevance of caspases could be proven, revealing different roles in individual cell lines. In the PDAC cell line Colo357 we demonstrated activation of p38, ERKs, JNK and NF-κB by death ligands, CD95L and TRAIL, leading to non-apoptotic proinflammatory effects. Inhibition of caspases by zVAD strongly diminished the CD95L- and TRAIL-induced proinflammatory response and strongly inhibited p38, ERKs, JNK and NF-κB. Different results were obtained with other PDAC cells: Panc-Tul showed death ligand-induced non-apoptotic signaling together with activation of the same signal molecules, except for ERKs, but revealed a strong enhancement of proinflammatory responses after inhibition of caspases, accompanied by enhanced JNK and NF-κB signaling (Siegmund et al., 2007). Recruitment of FADD, caspase-8, FLIP, TRAF2 and RIP to the DISC was similar in both cell types. Thus, an ERK- and NF-κB-stimulating, caspase-dependent factor can be postulated to operate downstream of the DISC in the Colo357 cells. It has been shown that the DISCs of TNF-R family members are internalized upon ligand binding. This was demonstrated for TNF-R1 (Schneider-Brachert et al., 2004) as well as for CD95 (Lee et al., 2006). The latter also exhibited different mechanisms for pro-apoptotic and non-apoptotic signaling, respectively. In type I cells signaling events of the non-apoptotic cascade, as phosphorylation of ERK1/ERK2 and NF-κB activation, do not require CD95 internalization, whereas internalization is mandatory for apoptosis induction. These studies also clearly show that several components of receptor complexes are not initially bound, but are recruited subsequently after endosomal internalization. Similar investigations of TRAIL-mediated responses revealed further complexity since it has been recently shown that TRAIL signaling may engage not only homotypic receptors, but also receptor-heteromers (R1/R2 and R2/R4). Moreover, only two TRAIL-receptors, R1 and R2, are able to induce cell death, whereas the other receptors, R3 and R4, inhibit cell death (Merino et al., 2006; Pennarun et al., 2010). Yet, investigations of PDAC cell lines had demonstrated that these cells express at the cell surface TRAIL-R1 and TRAIL-R2 whereas TRAIL-R3 and -R4 are hardly detectable (Ibrahim et al., 2001; Lemke et al., 2010; Trauzold et al., 2003a). Up to now, only little is known about the biochemical behavior of TRAIL-R1 and –R2 in tumor cells. It was shown that TRAIL-R2-carrying human fibrosarcoma cells form primary TRAIL-DISCs and also contain secondary signaling complexes that are possibly responsible for non-apoptotic signaling (Varfolomeev et al., 2005). Whether these results also relate to the findings of Lee et al. on CD95 recepotosomes (Lee et al., 2006) remains to be shown. Another report proposed a differential caspase-dependent regulatory relationship between TRAIL receptor activation, its clathrin-dependent endocytosis, and cell death (Austin et al., 2006). The authors suggested a model, by which TRAIL-R2 endocytosis antagonizes pro-apoptotic signaling in case of low caspase activation. However, at high initial caspase activation, e.g. in susceptible type I cells, TRAIL receptor endocytosis is inhibited, thereby amplifying caspase activation and apoptosis. The validity of this model for type I versus type II cells is still unclear. Generally, differential receptor involvement and/or subsequent different signaling complexes or compartmentalization of signaling events must be regarded as extremely important issues, as was analogously demonstrated for a receptor system in immune cells (Daniels et al., 2006; Palmer and Naehler, 2009). Here, the authors showed that small differences in an analog input parameter (i.e. ligand affinity) could be converted into a digital output, i.e. a decision in favor of a specific signal pathway.

**Conclusion**

Taken together, CD95L, TRAIL and TNF can promote both, apoptosis and non-apoptotic functions (proliferation, inflammation and migration/invasion), but depending on the cellular context, individual steps in the complex signaling chains may be inefficient or blocked. As a consequence, this will shift the net balance of cellular homeostasis towards apoptosis or, as for many tumor cells, survival and a higher malignancy. However, a detailed understanding of the molecular mechanisms and the interplay between pro-apoptotic and non-apoptotic signaling pathways is still missing.

From a clinical point of view this model points to the necessity to very carefully evaluate the possible in vivo “side effects” of death receptor agonists like TRAIL before being therapeutically administered and to select therapeutic schemes that not only aim to induce apoptosis, but also prevent pro-invasive and pro-inflammatory non-apoptotic signaling.

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