Aberrant expression and function of death receptor-3 and death decoy receptor-3 in human cancer (Review)

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Abstract. Death receptor-3 (DR3) and death decoy receptor-3 (DcR3) are both members of the tumour necrosis factor receptor (TNFR) superfamily. The TNFR superfamily contains eight death domain-containing receptors, including TNFR1 (also called DR1), Fas (also called DR2), DR3, DR4, DR5, DR6, NGFR and EDAR. Upon the binding of these receptors with their corresponding ligands, the death domain recruits various proteins that mediate both the death and proliferation of cells. Receptor function is negatively regulated by decoy receptors (DcR1, DcR2, DcR3 and OPG). DR3/DcR3 are a pair of positive and negative players with which vascular endothelial growth inhibitor (VEGI) interacts. VEGI has been suggested to be a potential tumour suppressor. The inhibitory effects of VEGI on cancer are manifested in three main areas: a direct effect on cancer cells, an anti-angiogenic effect on endothelial cells, and the stimulation of dendritic cell maturation. A recent study indicated that DR3 may be a new receptor for E-selectin, which has been reported to be associated with cancer metastasis. DcR3 is a soluble receptor, highly expressed in various tumours, which lacks an apparent transmembrane segment, prevents cytokine response through ligand binding and neutralization, and is an inhibitor of apoptosis. DcR3 serves as a decoy receptor for FasL, LIGHT and VEGI. The cytokine LIGHT activates various anti-tumour functions and is expected to be a promising candidate for cancer therapy. Certain tumours may escape FasL-dependent immune-cytotoxic attack by expressing DcR3, which blocks FasL function. DR3/DcR3 play profound roles in regulating cell death and proliferation in cancer. The present review briefly discusses DR3/DcR3 and attempts to elucidate the role of these negative and positive players in cancer.

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Contents

1. Introduction

Death receptor-3 (DR3) was first identified in 1996 (1-3) and was named Apo-3; it is also termed as LARD, TRAMP, WS-1, TR3 and TNFRSF25. DR3 was found to be a transmembrane protein of approximately 47 kDa sharing similar extra-cellular cysteine-rich domains with other members of the tumour necrosis factor receptor (TNFR) family. In addition, DR3 resembles TNFR1 and CD95, in that it contains a cyto-plasmic death domain. DR3 was thought to be the receptor for TWEAK in an early experiment (4), but later studies disproved this hypothesis (5,6).

Currently, DR3 is known as the functional receptor of vascular endothelial growth inhibitor (VEGI) (7,8). Recent studies have revealed a profound implication of VEGI in clinical cancer. The expression and effects of VEGI have been investigated in a wide variety of human cancer cell lines, including breast, prostate, bladder, colorectal and liver cancer cells (9). However, the mechanism of action of VEGI in cancer remains unclear. Activated DR3 has been shown to induce rapid apoptosis by activating the caspase cascade through inter-action with TRADD and FADD (1-3,10,11). Like other TNFR family members, DR3 is also able to induce nuclear factor κB (NF-κB) and to promote cell survival signals via TRADD and TRAF2 (2,8,11,12). However, a recent study showed that DR3 may be a new receptor for E-selectin, which has been linked with cancer metastasis. The findings of this study indicate that the activation of DR3 in response to E-selectin triggers the transendothelial migration of cancer cells and protects them against apoptosis, suggesting that DR3 has evolved to provide metastatic advantages to colon cancer cells (13).

Death decoy receptor-3 (DcR3) was first detected in 1998 in human lung and colon tumours as a decoy receptor that

binds to FasL and inhibits FasL-induced apoptosis. It is also known as TR6 or M68 (14). Currently, DcR3 is known to be a soluble receptor and a secreted protein belonging to the TNFR superfamily, and is a decoy receptor for VEGI, FasL and LIGHT (8,14-16). DcR3 lacks transmembrane and cytoplasmic domains in its sequence. Wu *et al* found that serum DcR3 was negative in 97.9% (47/48) of healthy individuals and patients with acute infection and positive in 56% of tumour patients, while >70% of patients with gastric, liver and gallbladder carcinomas had elevated serum DcR3 levels (>20 pg/ml) (17). Tumour cells engineered to release high amounts of DcR3 are protected from apoptosis and chemotaxis, which in turn results in a decreased immune response to the TH2 phenotype (18-21). This suggests that DcR3 is involved in the progression and immune evasion of malignant tumours.

2. Structure of DR3 and DcR3

DR3 is a transmembrane protein of which at least 11 distinct isoforms, generated by alternative splicing, exist. The major isoform has a molecular weight of 47 kDa (22). The DR3 gene has been mapped to human chromosome 1p36.3 (2,3). DR3 protein has a signal sequence (amino acids 1-24), followed by an extracellular region (amino acids 25-198), a transmembrane domain (amino acids 199-224) and an intracellular region (amino acids 225-417). The extracellular domain (ECD) contains four cysteine-rich pseudorepeats which resemble the corresponding regions of human TNFR1 (four repeats) and CD95 (three repeats). The intracellular domain (ICD) contains a sequence which resembles the death domains found in the ICDs of TNFR1 and CD95 and in other death signaling proteins, such as human FADD/MORT1, TRADD, RIP and Drosophila Reaper. Notably, four out of the six amino-acid residues in the death domain of TNFR1 that are essential for signaling [F345, R347, L351 and W378 (23)] are identical in DR3 (F350, R352, L356 and W382), whereas the remaining two TNFR1 residues [E369 and 1408 (23)] are semi-conserved in DR3 (D371 and L409). The sequence homology between DR3 and TNFR1 is particularly high: 40% in the death domain and 22% in the extracellular cysteine-rich domain (22).

In 1998, Pitti *et al* isolated a previously unknown full-length complementary DNA from human fetal lung (14), and named the protein encoded by this cDNA DcR3. The DcR3 gene was mapped to human chromosome 20q13. The cDNA encodes a 300-amino-acid polypeptide which belongs to the TNFR family (14). The amino terminus contains a leader sequence, which is followed by four tandem cysteine-rich domains (CRDs). This is similar to another TNFR homologue, osteoprotegerin (OPG) (24). DcR3 is a protein with a relative molecular mass of 35 kDa and lacks an apparent transmembrane sequence. All of the cysteines in the four CRDs of DcR3 and OPG are conserved; however, the carboxy-terminal portion of DcR3 is 101 residues shorter.

3. Ligands of DR3 and DcR3

VEGI is a recently identified anti-angiogenic cytokine that was first detected in 1999 in human umbilical vein endothelial cells, and belongs to the TNF superfamily. VEGI is also known as tumour necrosis factor superfamily member 15 (TNFSF15) and TNF ligand-related molecule 1 (TL1) (7,25). VEGI binds to DR3 and subsequently triggers intracellular events, which can be blocked by DcR3. VEGI has been extensively studied in immune disorders. Recent investigations have highlighted a potential cancer inhibitory role for this cytokine. The inhibitory effects of VEGI on cancer are manifested in three main areas: direct inhibition of cancer cell proliferation, anti-angiogenic effects on endothelial cells and the stimulation of dendritic cell maturation. VEGI is able to inhibit the growth of various human tumour cell lines, including human histiocytic lymphoma (U-937), human breast carcinoma (MCF-7), human epithelial carcinoma (HeLa) and human myeloid lymphoma (ML-1a) (26). VEGI was also shown to inhibit tumour growth *in vivo* and to suppress the growth of colon carcinoma cells (murine colon cancer cells, MC-38) both *in vitro* and *in vivo* (7,27,28). Parr *et al* reported that patients with breast tumours expressing reduced levels of VEGI had a higher local recurrence, shorter survival time and an overall poorer prognosis than those patients expressing high levels of VEGI. In addition, VEGI levels were lower in lobular tumours compared to tumours of ductal origin (9). However, it is unclear whether other mechanisms, such as activation of tumour-specific or non-specific B or T lymphocytes or induction of cytokines (29), are also involved in VEGI-mediated tumour suppression.

E-selectin (CD62E, ELAM-1, LECAM-2) belongs to the selectin family, which features calcium-dependent type I transmembrane glycoproteins with extracellular lectin-like domains (30). It is specifically synthesized by endothelial cells and is not constitutively present. E-selectin is transcriptionally regulated by several transcription factors, such as tumour necrosis factor α (TNFα), interleukin (IL)-1, NF-κB and activator protein 1 (AP-1) (31,32). Once expressed on the cell surface, E-selectin is slowly internalized and directed to lysosomes for degradation (33). Two major glycoprotein receptors for E-selectin have been identified: the E-selectin ligand-1 (ESL-1) and P-selectin glycoprotein ligand-1 (PSGL-1) (34,35). DR3 has been suggested as a new receptor for E-selectin which has been linked to cancer metastasis (13). The usual role of E-selectin is to mediate the adhesion of leukocytes to the endothelium allowing their extravasation into inflamed tissues. Inflammation and cancer metastasis are associated with extravasation of leukocytes or tumour cells from blood circulation into tissue. E-selectin, in part, is involved in these processes (36-42).

LIGHT, a member of the TNF superfamily, is produced as a glycosylated 29-kDa type II transmembrane protein by activated T cells, monocytes, granulocytes and immature dendritic cells (43). Its name is derived from homology to the lymphotoxins. LIGHT exhibits inducible expression and competes with herpes simplex virus glycoprotein D for herpes virus entry mediator, a receptor expressed by T lymphocytes. LIGHT binds to two functional cellular receptors, lymphotoxin β receptor (LTβR) and herpes virus entry mediator (HVEM), as well as to a non-functional soluble DcR3 (44,45). The cytokine LIGHT activates various anti-tumour functions through the activation and augmentation of tumour immunity via LTβR and HVEM, and is expected to be a promising candidate for cancer therapy (46-49). DcR3 neutralizes the

biological effects of LIGHT and contributes to immune escape of tumours by binding to LIGHT.

FasL, Fas ligand (also known as CD95L), a type II membrane protein, belongs to the TNFR family (50,51). FasL induces apoptosis upon receptor/ligand engagement. Fas/FasL-mediated apoptosis is a normal and important homeostatic mechanism involved in the down-regulation of hyperimmune responses and the removal of activated lymphocytes (52). During carcinogenesis, tumour cells develop many mechanisms to subvert the immune system and suppress the anti-tumour immune response, among which Fas and FasL molecules play an important role in immune escape (53). It has been shown that cancer cells, such as breast, colon, gastric and esophageal carcinoma, may counterattack FAS-sensitive tumour-infiltrating lymphocytes (TILs) via highly expressed FASL. This mechanism may lead to a tumour cell immune privilege that sequentially contributes to cancer formation and progression (54-58). DcR3 is a decoy receptor for FasL. Overexpression of DcR3 in tumours may be beneficial in terms of protecting against the cytotoxic and regulatory effects of FasL (14). Recent studies have shown a significant correlation between the expression levels of DcR3 and FasL-inducing apoptosis (59).

4. Expression and cell/tissue distribution of DR3/DcR3

DR3 is preferentially expressed in peripheral blood leukocytes and in lymphocyte-rich tissues, including thymus and spleen, and to a lesser extent in the small intestine, colon, fetal lung, bone, ovary, brain, peripheral nervous system and fetal kidney (1,2,25,60-63). Some tumour cells also express DR3 (25,63,64). DR3 may be expressed in multiple forms by alternative splicing, for example osteoblasts express both transmembrane and soluble forms of DR3 (60). DcR3 is known as a soluble receptor. DcR3 expression has been noted in diverse tissues, including the colon, stomach, spleen, lymph node, spinal cord, pancreas and lung (14,15). Compared to normal tissue, DcR3 is overexpressed in malignant tumours from various organs, such as nasopharyngeal esophagus, laryngeal stomach, kidney, colon, liver, ovary and pancreas (15,65-72).

Lupeol (Lup-20(29)-en-3H-ol), a novel dietary triterpene, was found to specifically cause a significant decrease in the expression of DR3 mRNA and protein and a significant elevation in expression of FADD mRNA in hepatocellular carcinoma SMMC7721 cells (73). Hayashi *et al* found that TNFα increased DcR3 expression and inhibited Fas-induced apoptosis in rheumatoid arthritis from patients with fibroblast-like synoviocytes (74). Another study demonstrated that insulin-like growth factor-1-induced activation of the phosphatidylinositol 3-kinase (PI3K)/Akt/NF-κB signaling pathway is involved in the modulation of endogenous DcR3 expression in AsPC-1 cells, and reduced endogenous DcR3 levels increase FasL-induced apoptosis of human pancreatic cancer cells (69).

5. Functions of DR3/DcR3

The precise role and mechanism of DR3 in a physiopathologic context remains unclear. DR3 induces cellular apoptosis and proliferation via activation of the caspase apoptotic cascade or the transcription factor nuclear factor-κB (NF-κB), stress-activated protein kinase (SAPK), c-Jun N-terminal protein kinase (JNK) and p38 mitogen-activated protein kinase (MAPK). DR3 contains a cytoplasmic death domain (DD), sharing certain similarity with TNFR1 and CD95. The signaling pathways induced by these receptors are similar and rely on the oligomerization of the receptors. Upon binding with ligands, recruitment of death domain proteins, such as TRADD, FADD, TNF-receptor associated factor-2 (TRAF2), LICE (FADD-like interleukin 1β-converting enzyme) or RIP1, through homophilic interaction of their death domains subsequently activate the caspase apoptotic cascade or the NF-κB pathway (2,11,22). Constitutive activation of DR3 is prevented by interaction with the silencer of death domains (SODD) (3). Activation of DR3 by VEGI induces caspase activation and apoptosis in TF-1, human histiocytic lymphoma (U-937), human breast carcinoma (MCF-7), human epithelial carcinoma (HeLa) and human myeloid lymphoma (ML-1a), but not in T cells (8,26). VEGI binding to DR3 functions as a T cell co-stimulator, and VEGI production in monocytes leads to enhancement of T cell responses (8,75). However, Wen *et al* reported that the binding of TL1A to DR3 activated both the NF-κB and ERK pathway, while JNK and apoptosis-inhibiting protein c-IAP2 prevented DR3-mediated apoptosis in TF-1 cells. In this context, TL1A induces apoptosis in the presence of cycloheximide which subsequently blocks the synthesis of c-IAP2 (12). A recent study suggested that DR3 is an E-selectin receptor on colon cancer cells. Its activation by E-selectin triggers the activation of p38, extracellular signal-regulated kinase (ERK), MAPK pathways, and confers migration and survival advantages to cancer cells. DR3 is a death receptor, but its activation by E-selectin does not induce apoptosis in colon cancer cells, except when ERK is inhibited (13).

DcR3 transducer antagonizes DR3-mediated apoptotic signals and other functions via competitive binding with VEGI, FasL and LIGHT (8,59,76-78). Moreover, Hsu *et al* demonstrated that DcR3 is capable of inducing actin reorganization and enhancing the adhesion of monocytes and THP-1 cells by activating multiple signaling molecules, such as protein kinase C (PKC), PI3K, focal adhesion kinase (FAK) and Src kinases. This suggests that soluble DcR3, similar to other immobilized members of the TNFR superfamily, is able to trigger 'reverse signaling' to modulate cell function (20).

6. Implications of DR3/DcR3 in carcinoma

The roles played by DR3 in cancer are controversial. Tian *et al* reported that endothelial progenitor cells (EPCs) play a critical role in postnatal and tumour vasculogenesis. VEGI inhibits endothelial cell proliferation by inducing apoptosis, and this may be inhibited by neutralizing antibodies against DR3 or the recombinant extracellular domain of DR3 (79). However, reduced expression of DR3 has also been noted in hepatocellular carcinoma cells (SMMC7721) undergoing apoptosis induced by the chemopreventive agent lupeol (73). However, a recent study reported that DR3 is a new E-selectin counter-receptor that confers migration and survival advantages to colon carcinoma cells by triggering p38 and ERK MAPK activation. They proposed that activation of DR3 by E-selectin acts as a switch that regulates metastasis by allowing colon carcinoma cells to escape apoptosis at the

benefit of migratory (p38) and survival (ERK) events (13). Fisetin, a natural flavonoid, inhibits DR3-mediated apoptosis and invasion in chemoresistant pancreatic cancer AsPC-1 cells induced by NF-κB (80). This suggests that DR3 may play crucial roles downstream of VEGI and other ligands in the regulation of survival and migration of cancer cells.

DcR3 inhibits cytotoxicity against tumour cells that is induced by Fas-FasL and LTβR-LIGHT signaling, and interferes with T cell co-stimulation mediated by HVEM-LIGHT association (14,74,81). Liang *et al* found a positive correlation of DcR3 with the differentiation of colorectal carcinoma cells, lymph node metastasis and pathological stage. The overexpression of DcR3 in colorectal cancer may contribute to the development of this cancer (67). DcR3 was also demonstrated as a predictive marker for 5-fluorouracil-based adjuvant chemotherapy in a study for colorectal cancer. In addition, expression of DcR3 in gastric carcinoma was found to be significantly higher compared to that in dysplasia, intestinal metaplasia and chronic superficial gastritis tissue. Moreover, DcR3 expression was found to correlate with local lymph node involvement and systemic metastasis (82,83). Gastric cancer patients with high DcR3 expression presented more advanced pN2-3 disease than those with low DcR3 expression. Pre-operative assessment of DcR3 expression may be an additional approach to imaging modalities for evaluating N stages in gastric cancer to guide operative procedures (84,85). Overexpression of DcR3 was found to be associated with resistance to Fas ligand-mediated apoptosis (86,87). Certain studies suggest that the expression of DcR3 may also be a useful prognostic factor in some types of cancers (70,88). In addition, DcR3 may have suppressive effects to down-regulate the host-immune system (89,90).

7. Perspective

Currently, little is known about DR3/DcR3 in cancer, particularly their potential as anti-tumour targets. Upon binding to DR3, VEGI was found to directly stimulate mouse dendritic cell maturation, which is an essential component of host immunity against cancer development (91). VEGI serves as a potential target in the development of angiogenesis-based cancer therapy. In contrast to the function of DR3, soluble DcR3 is generated to interfere with the autocrine function of VEGI (78). Enhanced expression of DcR3 has been indicated in various solid tumours. This protects cancer cells and vascular endothelial cells from induced apoptosis and is positively correlated with tumour progression.

Further investigation of DR3/DcR3 and the associated signal pathways may expand the understanding of their role in cancer. This may provide a basis for tumour selective therapeutic targets, particularly for those associated with a defect in DR3/DcR3 signaling. Interest in DR3/DcR3 is increasing. Recently, Morishige *et al* constructed DcR3-evading LIGHT mutants that may be powerful tools for cancer therapy (92). Wu *et al* generated monoclonal antibodies (mAbs) against human DcR3 for the study of DcR3 expression, distribution in tissue and development of an ELISA kit (93).

In summary, the aberrant expression and function of DR3/DcR3 has been implicated in carcinoma. DR3/DcR3 is related to several ligands which have the ability to affect apoptosis, angiogenesis and immune escape of tumours. Future studies should focus on elucidating their role in cancer under both physiological and pathological conditions. These findings may be useful for the diagnosis, differentiation, metastasis and determination of cancer stages. Furthermore, these may provide novel therapeutic approaches for targeting carcinomas in the future.

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