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Review

The Role of Decoy Receptor DcR3 in Gastrointestinal Malignancy

STYLIANI LAGOU[1], DIMITRA GRAPSA[1], NIKOLAOS SYRIGOS[1] and GEORGIOS BAMIAS[2]

[1]Oncology Unit, 3rd Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Athens, Greece;
[2]GI Unit, 3rd Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Abstract. *Malignancies are among the leading causes of mortality worldwide. Early detection and treatment are the primary targets of clinical and translational research, and may be facilitated by the recognition of novel diagnostic and prognostic biomarkers. Decoy receptor 3 (DcR3) is a soluble receptor of the tumor necrosis factor receptor superfamily of proteins (TNFRSF), which associates with its respective TNF-like ligands, Fas-L, LIGHT, and TL1A. DcR3 has been recognised as a significant anti-apoptotic factor with prominent involvement in various inflammatory and neoplastic conditions. Increased intratumor expression of DcR3 and elevated soluble DcR3 protein content in the sera of patients has been reported for various malignancies. Recent published work has suggested that monitoring of local and systemic DcR3 may provide an attractive biomarker, mainly for defining subgroups of patients with aggressive tumor behaviour and poor prognosis. The aim of the present review is to summarize and critically present existing evidence regarding the potential clinical importance of monitoring DcR3 expression in patients with malignancies of the gastrointestinal tract, as well as liver and pancreatic cancer. We also present a detailed description of the pathophysiological basis that may underlie the involvement of DcR3 in gastrointestinal carcinogenesis. Based on these data, we comment on the potential applicability of DcR3 monitoring in the diagnosis and, most importantly, the prognostic stratification of patients.*

Correspondence to: Dimitra Grapsa, MD, Ph.D., Oncology Unit, 3rd Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Athens, Greece. Tel: +30 2107475034, e-mail: dimgrap@yahoo.gr

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Decoy receptor 3 (DcR3) was originally described in 1998 as a novel member of the tumor necrosis factor receptor superfamily (TNFRSF) (1). This protein has been also referred in the literature as TNFRSF6B, TR6, or M68. DcR3, along with DcR1, DcR2, and osteoprotegerin (OPG), constitute a distinct subset within the TNFRSF, namely the decoy receptor family (2). In fact, DcR3 and OPG share high protein sequence homology and are unique among TNFRSF members in that they solely exist as secreted, soluble proteins, since they lack a transmembrane domain (2).

DcR3 protein is encoded by the *Tnfrsf6b* gene that is located at the extreme telomere of human chromosome 20 (20q13.3). The translational product is a protein of 300 amino acids (NCBI accession #NM_032945). Polymorphisms in the *Tnfrsf6b* gene have been associated with modified risk for sporadic IgA nephropathy and paediatric-onset inflammatory bowel disease (3, 4). Mouse and rat genomes lack a *Tnfrsf6b* gene, thus, imposing difficulties in pre-clinical translational research regarding the role of DcR3 in clinical conditions.

DcR3 is a prototypic decoy receptor, which is capable of binding to and interacting with three ligands of the TNF superfamily of proteins. In particular, DcR3 binds to Fas ligand (TNFSF6), LIGHT (receptor homologous to lymphotoxins that exhibits inducible expression, competes with HSV glycoprotein D for the HVEM, and is expressed by T lymphocytes) and TNF-like molecule 1A (TL1A) (1, 5, 6). The decoy function of Dcr3 is primarily exerted when DcR3

competes with the functional receptors for binding to the respective cytokines (Fas for FasL, DR3 for TL1A, and LTbR and herpesvirus entry mediator/HVEM for LIGHT), thus preventing downstream signaling. Functional signaling *via* these cytokine/receptor pairs have been shown to be critically involved in apoptotic and immunomodulatory pathways. Accordingly, DcR3, by inhibiting these effects, has been described as a potential regulator of carcinogenesis (*via* inhibition of apoptosis) and immunological responses (*via* preventing the immunostimulatory effects of its ligands) (7). Nevertheless, it has been shown that DcR3 may also exert several "non-decoy" functions through direct (or even reverse-ligand) signalling, further affecting immunological pathways. In line with these data, over-expression of DcR3 has been demonstrated in several neoplastic and inflammatory diseases. In addition, it has been proposed that its manipulation may offer therapeutic options in such clinical scenarios.

The current review focuses on the role of DcR3 in malignant tumors of the gastrointestinal (GI) system, including pancreatic and liver cancer. In fact, there is a growing number of reports that support the notion that DcR3 is associated with the development and prognosis of GI tumors. In particular, a meta-analysis that was conducted in 2014, on 28 studies with 3,294 patients, albeit exclusively from China and Japan, reported an association between DcR3 and various clinicopathologic features, such as TNM stage, differentiation, lymph node metastasis, infiltration degree, metastasis in patients with GI tumors (8). In this review, we first present experimental data that indicate an involvement of this decoy receptor in the mechanisms that may underlie carcinogenesis of the GI system. In the second part, we present the clinical evidence that supports the potential significance of DcR3 as a diagnostic and prognostic marker in these diseases.

Pathophysiological Mechanisms

Accumulating clinical data (see below in Clinical Relevance) clearly indicate that DcR3 is highly up-regulated in malignant neoplasms of the GI tract and may also be associated with aggressive disease, thus, serving as a prognostic factor for unfavorable outcomes. Such associations also insinuate that DcR3 may be pathogenetically involved in the pathways that underlie tumor development and progression; this hypothesis has been intensively investigated. Most experimental data on the role of DcR3 in carcinogenesis are derived from *in vitro* studies with cancer cell lines. This is somewhat a research necessity, as mice and rats do not express DcR3, making mechanistic, *in vivo* studies impossible. In studies with cancer cell lines, however, it was clearly shown that over-expression of DcR3 induces the neoplastic potential, whereas, its elimination results in the opposite effect. Interestingly, these effects were preserved across cell lines of various tissue origins. This points to common DcR3-mediated pathways that interfere with the carcinogenesis, taking place at different organs of the GI tract.

DcR3 has been traditionally considered an anti-apoptotic protein because it acts as a decoy receptor for TNFSF members that are involved in the induction of programmed cell death (9). In particular, its role as a competitor/inhibitor of Fas/FasL signaling has been well-established as a central mechanism through which DcR3 increases the survival of malignant cells. Tsuji *et al*. (10) examined several pancreatic cancer cell lines and found that treatment with an agonistic anti-Fas antibody or exposure to membrane-bound FasL resulted in growth inhibition of cells, following pre-treatment with IFN-g. Exogenous DcR3, however, reversed such inhibition, interfering with sensitivity to membrane-bound FasL. In another study, Chen *et al*. (11) used AsPC-1 human pancreatic adenocarcinoma cells to show that silencing of DcR3 was a prerequisite for the induction of FasL/Fas-mediated cell death. This was also shown by Zhou *et al*. (12), who used small interfering RNA (siRNA) to knockdown the expression of the DcR3 gene in pancreatic cancer cell lines and showed that this resulted in augmentation of apoptosis regulated by Fas, caspase-3, and caspase-8. Similar effects were also shown in liver cancer HepG2 cells, whereby an increase in cell apoptosis *via* FasL/Fas signaling was observed after DcR3 silencing *via* targeting by lentivirus-based short hairpin RNA vector or miR-340 mimics (13, 14). It should also be noted that, besides affecting the apoptotic pathways *per se*, DcR3 may also affect the responsiveness of tumor cells to chemotherapy. Along this line, it was shown that knockdown of DcR3 by RNA interference enhanced the sensitivity of gastric cancer cells to 5-FU (15). The temporal evolution of DcR3 expression during tumorigenesis has also been reported in a murine model of hepatocellular carcinoma (16). In this model, Fas expression was detected before that of DcR3; nevertheless, this was followed by disappearance of the former and persistence of the latter. Therefore, although DcR3 may be initially triggered as a response to amplification of the apoptotic machinery, in later phases it may supersede these pathways, leading to immunological tolerance. Besides the Fas/FasL pathway, DcR3 may also interfere with additional apoptotic pathways, as it was shown that it can counteract the death-promoting function of TRAIL. This was first demonstrated in pancreatic cancer cells, which highly produce DcR3. In particular, endogenous DcR3 may inhibit TRAIL-mediated apoptosis, whereas silencing of DcR3 resulted in the re-establishment of this apoptotic pathway (17). These results were later recapitulated by two independent groups in human liver cancer HepG2 cells (18). Taken together, the aforementioned findings clearly indicate that a principal mode of involvement of DcR3 in carcinogenesis relates to its high endogenous production by cancer cells and its ability to, subsequently, reverse growth inhibition signals that are

generated by apoptotic pathways, including those mediated by Fasl or TRAIL.

DcR3 may also affect carcinogenesis through its immunomodulatory effects on macrophages, in particular, tumor associated macrophages (TAMs). During the progression of tumorigenesis, a shift in TAM phenotype was shown to take place (19, 20). During the initial tumor appearance, TAMs display an M1, pro-inflammatory-dominant, "high IL-12/low IL-10" phenotype that boosts anti-tumor immunity. At later stages, however, M2 macrophages prevail, which demonstrate an immunosuppressive phenotype characterized by low pro-inflammatory cytokine secretion and elevated production of TGF-b1. These changes create a microenvironment that favors tumor survival and growth. Previous studies have shown that DcR3 may favor the differentiation of macrophages to an M2 phenotype. In a first study by Chang *et al*. *(*21) it was shown that treatment with a DcR3.Fc fusion protein modulated the phenotype of macrophages including down-regulation of CD14, CD16, CD64, and HLA-DR and impairment of their phagocytic capacity against immune complexes and apoptotic bodies and the production of free radicals and proinflammatory cytokines in response to lipopolysaccharide (LPS). Interestingly, these functions were not exerted *via* binding to FasL, LIGHT, or TL1A, but were dependent on membrane cross-linking, once more emphasizing the occurrence of "non-decoy" properties of DcR3. In further studies, the same group applied a micro-array methodology to study the effects of DcR3 on macrophages (22). It was found that DcR3 epigenetically affected the expression of genes that encode for constituent proteins of the MHC-II related pathway of antigen presentation, including the master class II trans activator, CIITA. The translational implication of these data was demonstrated by the significant correlation between DcR3 and reduced HLA-DR levels on TAMs from pancreatic cancer tissue. To provide mechanistic data on the pro-neoplastic role of DcR3, the same researchers developed a DcR3-Tg mouse and studied tumorigenesis *in vivo* in this strain (23). They report that DcR3-Tg mice displayed significantly enhanced tumor growth and spreading, which were associated with alterations in TAMs, as macrophages isolated from DcR3-Tg mice had an immunosuppressive, M2-like phenotype with increased production of IL-10, and IL-1ra, and reduced production of pro-inflammatory factors such as IL-12, TNF-a, IL-6, NO. The down-regulation of MHC-II was also confirmed. Besides TAMs, DcR3 may also negatively affect the antitumor properties of other cell types, as it was recently shown for double negative CD3+CD4-CD8- T-cells (24).

The exact intracellular mechanisms that mediate the effects of DcR3 on tumorigenesis are not well described yet. Downstream effects, which have been reported in the literature, include the activation of the TGF-b1/Smad2 signal transduction pathway and phosphorylation of Smad2, and a regulatory effect on the expression of MMP9, VEGF-C, and VEGF-D (13, 14). Finally, RNAi knockdown of DcR3 in SW1990 cells resulted in elevated expression of caspase 3, 8, and 9, and reduced ERK1/2 phosphorylation (25). DcR3 has also been shown to induce epithelial-mesenchymal transition (EMT) of tumor cells. This effect was shown in gastric cancer cell lines and it was mediated *via* DcR3-induced activation of the PI3K/AKT/GSK-3β/β-catenin signaling pathway (26). A similar effect was seen in colorectal cancer cells, where it involved downstream activation of TGF-β3/SMAD signaling (27). DcR3 was also shown to promote cancer cell migration, alongside cytoskeleton remodeling and inhibition of E-cadherin expression (28). These effects were associated with IκBα degradation and p65 nuclear translocation.

Similarly, the regulation of DcR3 expression in tumor cells remains elusive at the moment and may be affected by the specific cellular origin. In a study on pancreatic adenocarcinoma cells, it was shown that the regulation of endogenous DcR3 was dependent on insulin-like growth factor-1 *via* downstream activation of the PI3K/Akt/NF-kB signaling pathway (11). Interestingly, in a recent study, the existence of a positive feedback loop of DcR3 autoregulation was proposed, which includes an initial DcR3-induced phosphorylation of signal transducer and activator of transcription 1 (STAT1) and increased expression of interferon regulatory factor 1 (29). The latter then increased the transcriptional activity of DcR3, further amplifying its expression. In the same study, DcR3 was also shown to promote the up-regulation of carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1).

In all, there is now ample evidence to support a central role of DcR3 in GI tumorigenesis. DcR3 expression is strongly up-regulated in cancer cells of various origins within the GI system. Once over-expressed, DcR3 competes with the functional receptors for binding to the apoptotic proteins Fas, TRAIL, and, possibly, TL1A. DcR3 eventually dominates binding and its decoy function leads to inhibition of apoptosis, allowing for tumor cell survival, proliferation and migration. In addition, through its "non-decoy" properties, DcR3 induces local immunosuppression, mainly by the expansion of M2 anti-inflammatory macrophages in the tumor microenvironment. This further enhances immune-escape by tumor cells the net result being the augmentation of the malignant potential. Overall, this central role of DcR3 in tumor-promoting processes, raises the possibility that this protein may represent a potential therapeutic target in malignancies of the GI tract.

Clinical Relevance

Under normal conditions, DcR3 is not regularly detected in the serum and tissues. In contrast, it is amplified and over-

expressed and, thus, can be detected locally and/or systemically, in patients with malignancies, autoimmune disorders or inflammatory diseases (8, 9). Apart from the pathophysiological implications that were mentioned above, this augmented expression holds the potential for the use of DcR3 as a diagnostic or prognostic tool in neoplastic conditions. In the following sections we present existing evidence for the association between DcR3 and the main types of gastrointestinal cancers (Table I) (29-41).

Oesophageal Cancer

Several published studies support an association between DcR3 and oesophageal cancer of diverse types, as well as with various precancerous conditions. In a first study, Li *et al*. (30) examined the expression of DcR3 in esophagectomy tissues from patients with a history of Barrett esophagus. They showed a correlation between DcR3 protein expression and severity of esophageal lesions, as well as with the degree of adenocarcinoma differentiation. However, there was no correlation between DcR3 and tumor size, clinicopathological stage, patient age or survival. In particular, by comparing the expression of DcR3 between normal tissues, precancerous lesions of different grades, and esophageal adenocarcinoma, it was concluded that the percentage of positive cells and the staining intensity of DcR3 were proportional to the severity of the esophageal lesions. Over-expression of DcR3 was noted mainly in areas with high-grade dysplasia, carcinoma *in situ,* and adenocarcinoma, in contrast with benign esophageal mucosa, Barrett esophagus, and low-grade dysplasia.

Xiong *et al*. (31) examined a possible correlation between expression of DcR3 and clinicopathological features in patients with esophageal squamous cell cancer (ESCC). Of 109 patients, over-expression of DcR3 mRNA was found in 80 tumours (73.4%) *vs*. 52 (47.7%) of corresponding normal tissues ($p<0.01$). Likewise, the expression of DcR3 protein in normal tissue was lower than that of matched tumor tissue. Both DcR3 mRNA and protein expression correlated with the presence of lymph node metastasis (pN stage), whereas only mRNA expression correlated with the extent of tumor invasion (pT stage). Specifically, patients with pN1 disease (n=18) had much higher ratio of DcR3 over-expression than those with pN0 disease (n=34) (50% *vs*. 17.6%, $p=0.014$).

Finally, Ao *et al*. (32) examined the expression of DcR3, as well as a possible correlation between DcR3 and survival in patients with esophageal carcinoma. Eighty-two of 150 cases with esophageal cancer had positive DcR3 expression (expression rate: 54.67%). Analysis of Kaplan–Meier survival curves, revealed that the median survival of DcR3-negative patients was 62 months *vs*. 44 months in patients with positive DcR3 expression. This study further showed that DcR3 correlated with tumor size, lymph node metastasis, invasion degree, clinical stage but not with sex, age or degree of differentiation. Finally, higher DcR3 levels were associated with lower 3-year survival.

A recent genetic study showed that a specific polymorphism in the *Tnfrsf6b* gene may be associated with decreased apoptosis and enhanced invasive potential of malignant cells in ESCC (42). In two subsequent studies in Chinese patients, the authors examined the role of different polymorphisms of *Tnfrsf6b* in ESCC and found that some alleles were involved in carcinogenesis whereas others not (43, 44). Although existing genetic data are premature at the moment and require reproduction in larger and more diverse patient cohorts, the combination of gene polymorphism with expression patterns may provide a reliable tool in the future for the optimization of the management of patients with esophageal cancer.

Gastric Cancer

Two published studies have reported on the association between DcR3 and gastric cancer. Both studies, reached similar conclusions, inasmuch they reported that DcR3 is over-expressed in patients with advanced stage of disease and worse prognosis.

Takahama *et al*. (33) used paired samples of tumor and non-cancerous stomach tissues from 84 patients who were operated for gastric cancer in order to examine whether DcR3 has clinical relevance in association to the clinicopathological features of the tumor and patients' prognosis. Although DcR3 mRNA was detected in both tumor and noncancerous stomach tissues, the level of expression varied, with DcR3 mRNA being over-expressed in 22 of 84 (26%) patients with gastric cancer. DcR3 expression did not correlate with sex, age, tumor status, systemic metastases, and histological type. Nonetheless, DcR3 did correlate with metastasis to lymph nodes (35% of lymph node metastasis positive patients had significantly increased DcR3 levels compared to 11% of lymph node metastasis-negative patients, $p=0.03$) and tumor stage (DcR3 over-expressed in 8.7% of stage 1 tumors *vs*. 32.8% of stage 2-4 tumors, $p=0.02$). According to Kaplan–Meier survival curves, in a 63-month follow up, patients with DcR3 over-expression had a significantly shorter overall survival compared to those with normal levels of DcR3 ($p=0.016$), although this was not preserved in multivariate analysis.

Chen *et al*. (34) attempted to investigate the role of Dcr3 expression among different precancerous lesions and gastric tumors (gastric carcinoma, dysplasia, intestinal metaplasia and chronic gastritis). The authors reported variability in expression rates for the different types of lesions. Specifically, DcR3 over-expression was observed in only 2 of 42 cases of chronic superficial gastritis, followed by intestinal metaplasia (4/37) and dysplasia (7/45) and was significantly increased in gastric cancer (27/79). Well-differentiated tumors and limited

Table I. *DcR3 in gastrointestinal malignancies*.

Study	Tumor type	Population	Aim of study	Sample type	DcR3 detection method				Results	Comments
					PCR	ELISA	ICH	Western Blot		
Esophageal cancer										
Li *et al*. 2005 (30)	EAC	40 pts with Barrett 40 normal tissues 27 Barrett esophagus 27 low-grade dysplasia 22 high-grade dysplasia or carcinoma *in situ* 28 EAC	DcR3 expression in precancerous lesions and EAC	Tissues			+		DcR3 over-expression in high-grade dysplasia, *in situ* adenocarcinoma and EAC	DcR3 not associated: • tumor size • clinical - pathologic stage • age • survival
Xiong *et al*. 2010 (31)	ESCC	109 pts	Association between DcR3 and clinicopathologic features	Tissues	+		+		DcR3 mRNA associated: • tumor invasion • lymph node metastasis DcR3 associated: • lymph node metastasis	
Ao *et al*. 2013 (32)	Esophageal cancer	150 pts	DcR3's correlation with survival	Tissues			+		DcR3 correlated: • tumor size • lymph node metastasis • invasion degree • clinical stage • 3-year survival	DcR3 not associated: • sex • age • degree of differentiation
Gastric cancer										
Takahama *et al*. 2002 (33)	GC	84 pts	To evaluate DcR3's clinical relevance	Tissues	+			Northern blot	DcR3 associated: • lymph node metastasis* • pathological stage* • shortened OS *Associations was not significant statistically	DcR3 not associated: • age • sex • tumor size • metastatic status • histological type
Chen *et al*. 2008 (34)	GC	79 carcinomas 45 dysplasia 37 intestinal metaplasia 42 chronic gastritis	DcR3 expression in gastric precancerous lesions and carcinoma	Tissues			+		DcR3 was higher in: • gastric cancer pts • poorly differentiated specimens • TNM stage III-IV • node and systematic metastasis	DcR3 not associated: • age • sex • tumor invasion
Colorectal cancer										
Mild *et al*. 2002 (35)	CRC	294 pts	Role of DcR3 on survival in pts receiving adjuvant chemotherapy	Tissues	+		+		No significant correlation with DFS and OS with gene amplification or DcR3 protein overexpression (223pts) (multivariate analysis)	Adjuvant chemotherapy appeared to be more beneficial in patients with normal DcR3 gene copy number

Table I. *Continued*

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Study	Tumor type	Population	Aim of study	Sample type	DcR3 detection method				Results	Comments
					PCR	ELISA	ICH	Western Blot		
Liang *et al*. 2009 (36)	CRC	100 pts	Investigate DcR3 expression	Tissues	+		+	+	DcR3 mRNA and protein associated: • tumor differentiation • lymph node metastasis • Duke stage	DcR3 mRNA was significantly higher in cancer tissues
Zong *et al*. 2014 (37)	CRC	300 pts	Evaluate DcR3 as prognostic indicator				+		DcR3 correlated: • tumor differentiation • lymph node metastasis • TNM stage • OS	
Hepatocellular cancer										
Shen *et al*. 2005 (38)	HCC	48 pts	Evaluate DcR3 gene amplification and protein expression	Tissues	+		+		DcR3 associated: • apoptotic index • size of mass • stage • infiltration • metastasis	HCC occurrence not associated with gene amplification
Yang *et al*. 2010 (39)	HCC	67 pts HCC 8 cirrhosis 17 cholecystitis 28 controls	Clinical significance of DcR3	Serum Tissues		+	+		Serum DcR3 associated: • TNM stage • para-cirrhosis • capsular infiltration • metastasis recurrence of disease	Serum DcR3 elevated in pts with HCC or cirrhosis *vs*. controls
Pancreatic cancer										
Zhou *et al*. 2012 (40)	PC	50 pts	Clinical significance of DcR3	Serum Tissues	+	+	+		DcR3 mRNA correlated: • clinical stage • tumor size • lymph node • histological staging DcR3 protein and gene amplification correlated: • tumor size	
Zhou *et al*. 2014 (41)	PC	50 pts	DcR3's clinical and prognostic significance	Tissues Serum		+	+		DcR3 correlated: • lymph node metastasis • TNM stage	- Median OS for high DcR3 group was 16.3 months *vs*. 21.6 months for the low DcR3 group ($p<0.05$) - DcR3 was more elevated in pancreatic head carcinoma *vs*. cystadenoma and controls

Table I. *Continued*

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Study	Tumor type	Population	Aim of study	Sample type	DcR3 detection method				Results	Comments
					PCR	ELISA	ICH	Western Blot		
Wei *et al*. 2019 (29)	PC	112 pts 40 controls 64 patient tumor and non-cancerous tissues	DcR3's function and regulatory network	Tissues Serum	+	+	+	+	DcR3 correlated: • tumor size • lymph node metastasis • advanced clinical stage	Pts with high DcR3 exhibit shorter OS *vs*. those with low DcR3

CRC: Colorectal cancer; DcR3: Decoy receptor 3; DFS: disease-free survival; DSS: disease-specific survival; EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell cancer; HCC: hepatocellular carcinoma; IHC: immunohistochemistry; GC: gastric cancer; NET: neuroendocrine tumors; PC: Pancreatic cancer; PFS: progression-free survival; OS: overall survival; pts: patients.

disease (TNM stage I and II) seemed to express lower levels of DcR3 than poorly differentiated gastric cancers and extensive disease (TNM stage III and IV). Moreover, patients with no evidence of metastatic disease (in the lymph nodes or in distant organs) had significantly lower levels of DcR3 expression than those with lymph or systemic metastasis. No correlation was found in multivariate analysis between DcR3 expression and age, sex or the tumor invasive depth in patients with gastric cancer.

Despite the limited number of studies, the uniformity of these results support the hypothesis that DcR3 may be an indicator of aggressive behaviour in gastric cancer and, thus, hold the potential to serve as a biomarker.

Colorectal Cancer

Mild *et al*. (35) analysed data from a large randomized multicenter trial with patients that had received 5-fluorouracil/mitomycin C (5-FU/MMC) as adjuvant chemotherapy for colorectal cancer and investigated the association between *Tnfrsf6b* amplification and patient survival. In 63% of tumors (185/294), *Tnfrsf6b* was amplified; adjuvant chemotherapy was significantly more beneficial in patients with normal *Tnfrsf6b* gene copy number. The latter may play a role in selecting patients with colorectal cancer who may benefit from receiving adjuvant chemotherapy. In multivariate analysis, DcR3 amplification failed to be recognised as a prognostic factor of patient survival. In contrast, analysis of DcR3 protein over-expression had no significant correlation with patient survival and no predictive value in patients treated with adjuvant chemotherapy. This study raises the possibility that *Tnfrsf6b* gene copy number may serve as a predictive marker for defining the subset of patients who will mostly benefit from 5-FU/MMC adjuvant chemotherapy.

In a later study, Liang *et al*. (36) examined the expression of DcR3 mRNA and protein *via* RT-PCR, western blot, and immunohistochemistry in patients with colorectal cancer and the possible correlation with different clinicopathological factors. DcR3 mRNA and protein were both higher in colorectal cancer than in non-cancerous tissues, irrespectively of the method that was utilized for detection. The positive expression rate of immunoreactivity against DcR3 protein was 67% (n=100) in colorectal cancer tissues *vs*. 18% (n=100) in non-cancerous tissues. More specifically, DcR3 mRNA and protein levels, quantified by RT-PCR and western blot analysis, respectively, correlated with the degree of differentiation, lymph node metastasis and Duke's stage. Indeed, patients with poorly differentiated cancer types or positive lymph node metastasis or C/D Duke's stage had higher DcR3 mRNA and protein levels *via* all methods ($p<0.01$).

In a more recent study, Zong *et al*. (37) attempted to examine DcR3 expression as a potential prognostic factor for

colorectal cancer, in parallel with the expression of HER2. Of the 300 cancer cases examined, 58.33% showed DcR3 over-expression (*vs*. 18.33% with HER2). Alongside this over-expression, DcR3 significantly correlated with tumor differentiation, lymph node metastases, and pTNM stage ($p<0.05$). In contrast, HER2 associated only with tumor size. DcR3-positive status was associated with a poorer overall survival (OS) (median OS of 42.1 *vs*. 61.2 months for DcR3-negative status, HR=50.27, 95%CI=44.9-55.64, $p<0.001$). Even though HER2 positive status individually did not affect OS, double positive patients for HER2 and DcR3 had worse OS compared to those without DcR3 over-expression (median OS: 31.8 *vs*. 52.2 months, respectively, HR=35.1, 95%CI=22.04-48.16, $p=0.006$).

Furthermore, a recent study suggested that DcR3 expression may be consistent throughout the colon, whereas the expression of other biomarkers such as MUC2, MUC5AC, MUC6, CK7, and SATB2 may be diverse between different locations of the colon and different histological types of tumor (45).

Overall, data so far support an association between DcR3 and certain unfavourable clinical aspects of colorectal cancer. Its correlation with tumor invasion, lymph node metastases, and poor prognosis, point towards the potential role of DcR3 as a prognostic factor.

Hepatocellular Cancer

The association between DcR3 and liver cancer was studied by Shen *et al*. (38), who reported a 60.4% (n=48) ratio of DcR3 detection in patients with HCC, with no positivity in normal tissues. They also reported a correlation between DcR3 mRNA expression and different tumor-related parameters such as size of the mass, TNM stage, and infiltration or metastasis of the tumor ($p<0.05$), but no relationship with the membrane of the tumor, cancer embolus, and number of tumor nodes. In order to identify whether the underlying mechanism that led to the over-expression was the DcR3 amplification, they performed quantitative PCR on genomic DNA from all the patients. Amplification of the *DcR3* gene was 2-fold higher only in 7 of 48 tumor samples when *DcR3* mRNA expression was positive in 29 of 48 tumor samples. However, DcR3 protein expression was identified in only 5 cases of HCC by immunochemistry.

In another study, Yang *et al*. (39), measured DcR3 in the tissue and serum of patients with HCC in comparison to patients with cirrhosis or cholecystitis and normal controls. Serum DcR3 was elevated in patients with HCC or cirrhosis but not in the other groups. Moreover, serum concentrations of DcR3 increased proportionally with pTNM stage. Although a correlation between DcR3 levels in sera and immunochemistry was identified (r=0.472, $p<0.01$), the rate of DcR3 protein expression in HCC tissues was lower (61%, 39/64) than the corresponding percentage of DcR3 serum-positive patients (77%, 49/64). It is worth mentioning that a combination of AFP and DcR3 measurements was associated with a 93% sensitivity for HCC diagnosis, whereby single measurements performed substantially worse (AFP: 82%; DcR3: 76%).

Hepatocellular cancer usually develops on a background of liver cirrhosis. Thus, the expression of DcR3 was also looked for in patients with pre-cancerous conditions of the liver. These include viral hepatitis, liver fibrosis, cirrhosis, and fatty liver (46-49). Such studies showed a gradual progression of DcR3 expression from chronic viral hepatitis to cirrhosis and finally hepatocellular carcinoma (48). Such evolution of expression underlines the potential of DcR3 as a novel prognostic biomarker in clinical practice. In fact, DcR3 may facilitate early diagnosis of HCC in high-risk individuals with chronic liver diseases, and may also contribute to therapeutic decisions.

Pancreatic Cancer

Zhou *et al*. (40) investigated the expression of DcR3 mRNA and protein, as well as DcR3 gene amplification in 50 patients with pancreatic carcinoma. DcR3 mRNA was 5-fold higher in cancerous than in normal tissues, while the same trend was observed for gene amplification. DcR3 protein positive rate was 78% (n=50) for cancerous tissues *vs*. 24% (n=50) for normal pancreatic tissue. To identify the role of gene amplification, researchers divided the study population in two groups based on whether amplification was >2 times (n=21) or ≤2 times (n=29) and showed that the two groups were significantly different in both DcR3 mRNA levels and detection rates of DcR3 protein. DcR3 mRNA correlated with clinical PC staging, size of the tumor, lymph node metastasis and histological staging. DcR3 protein correlated with clinical PC staging and size of the tumor and DcR3 amplification correlated with tumor size only.

Two years later, the same investigators examined tissues and sera from patients with pancreatic head carcinoma, in order to investigate the correlation between DcR3 and different clinicopathological aspects, including prognosis (41). DcR3 levels in serum were elevated in patients with pancreatic head carcinoma compared to cystadenoma patients or healthy individuals and associated with DcR3 expression in tissues ($p<0.01$). The positivity rate of DcR3 in tumor tissues was 78% (n=50) *vs*. 24% (n=50) in paired normal tissues. Serum DcR3 levels correlated with lymph node metastasis and pTNM stage but not with any other parameter. The population study was divided in two groups based on DcR3 over-expression and univariate analysis showed that median OS for the high DcR3 group was 16.3 months *vs*. 21.6 months for the low DcR3 group ($p<0.05$). In multivariate analysis, DcR3 was recognised as an independent prognostic factor for OS along with tumor size, lymph node metastasis, and pTNM stage.

Wei *et al*. (29) evaluated the clinical significance of DcR3 gene amplification, DcR3 protein serum levels, and tissue expression of DcR3 in patients with pancreatic cancer. DcR3s transcripts, serum levels, and positivity rates in tissues were all elevated in cancer patients compared to matched controls. DcR3 over-expression correlated with larger tumour size (p=0.04), lymph node metastasis (p=0.037), and advanced clinical stage (p=0.01). Elevated DcR3 serum levels and over-expression in tissues resulted in significantly shorter OS compared to those exhibiting lower levels and positivity rates.

These three recent studies in patients with pancreatic cancer, although relatively small populated, are uniform in their reporting of a correlation between elevated DcR3 and aggressive tumor characteristics and/or poor prognosis.

Conclusion

The role of the anti-apoptotic protein DcR3 is gaining importance in oncology, due to its potential role as diagnostic, predictive, and prognostic marker. In regards to GI neoplasia, specifically, there is now converging evidence to associate elevated expression of DcR3 with advanced neoplasia both in the means of advance local tumor spread and distant metastasis.

From the pathophysiological perspective, involvement of DcR3 in GI carcinogenesis is mainly supported by its recognized anti-apoptotic function that is exerted via the inhibition of Fas/FasL, DR3/TL1A, and HVEM/LIGHT binding and downstream signalling. DcR3 may also amplify carcinogenesis through its immunomodulatory effects on tumor associated macrophages (TAMs). The combined effect of apoptosis inhibition in tumor cells with compromised immunosurveillance by macrophages creates a local microenvironment that may favor survival of malignant cells. The superimposed up-regulation of DcR3 expression by tumor cells further generates an amplification loop that may lead to further tumor growth, local invasion, and distant metastasis. Additional elucidation of the cellular and molecular modules that are involved in the propagation of such pro-neoplastic mechanisms would be essential to uncover the precise pathophysiological role of DcR3 in carcinogenesis. More importantly, it will reveal the true potential of this protein as a therapeutic target in GI malignancy.

From the clinical viewpoint, there are now several published reports that show elevated expression of DcR3 in neoplasms of the GI tract, especially malignancies. In the majority of cases, such increased expression is aligned with a more aggressive tumor profile, such as the presence of positive lymph nodes and distant metastasis. Unsurprisingly, in several studies, such characteristics culminate to adverse patient outcomes with shortened OS, when compared to patients who express normal levels of DcR3. It should be noted, however, that most studies suffer from methodological problems, and the prognostic value of DcR3 was not an independent factor for patient's survival. These shortcomings call for prospective studies that should be specifically designed to address the prognostic potential of DcR3 in GI malignancy.

In conclusion, the available data are still not sufficient to officially recommend the widespread use of DcR3 monitoring in GI neoplasia. Nevertheless, the combination of frequent and high up-regulation of DcR3 in different tumor types with the strong pathophysiological background for involvement in carcinogenesis pathways, justifies the further exploration of its applicability as a biomarker in oncology. Subsequent studies will better clarify the appropriate positioning of DcR3-centered diagnostic, prognostic, and therapeutic algorithms for cancers of the GI tract, liver, and pancreas.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

The Authors S.L. and D.G. drafted the paper; N.S. and G.B. revised the paper; All Authors approved the final article.

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