REVIEW

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DcR3 in All Its Aspects

Tüm Yönleriyle DcR3

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Abstract

Decoy receptor 3 (DcR3) is a supermember of tumor necrosis receptor (TNF) factor. DcR3 acts as a binding partner in multiple apoptotic ligands that inhibit apoptosis. TNF-associated apoptosis-inducing ligand (TRAIL)-induced apoptosis has been demonstrated to be sensitized by DcR3. DcR3 has been found to be a "pleiotropic" soluble factor with "decoy" and "non-decoy" activities that control cell functions. The connection between Fas and FasL can be inhibited by recombinant DcR3 coupled with an IgG1 Fc domain. TNF superfamily FasL can inhibit apoptosis and increase angiogenesis through neutralizing members of LIGHT and TL1A. DcR3 serum level is almost undetectable in most normal individuals without inflammatory diseases and cancer. According to several research, the level of DcR3 in the blood is linked to cancer stage in cancer patients. High DcR3 levels in serum or tissues have been found to be associated with poor prognosis and/or resistance to therapy in some cancer patients. As a result, identifying the cut-off value of the DcR3 serum level will provide to able to forecast the severity of disease in the future. While inhibiting DcR3 expression may slow tumor growth, improving DcR3-mediated effector functions could be a viable strategy for reducing autoimmunity and promoting tissue healing. Thus, recombinant DcR3 is a promising immunotherapeutic agent; yet, in the malignant environment, turning off DcR3 expression may improve cancer therapy success. The purpose of this review is to provide clinical convenience by collecting the findings of studies on DcR3 so far. These discoveries could help with cancer diagnosis, differentiation, metastasis, and stage detection. Furthermore, these may provide new therapeutic approaches to target carcinomas in the future.

Keywords: Biomarker, DcR3, DcR3 and cancer

Öz

Decoy reseptörü 3 (DcR3), tümör nekroz reseptörü (TNF) faktörünün bir üst üyesidir. DcR3, apoptozu inhibe eden çoklu apoptotik ligandlarda bağlayıcı bir ortak olarak görev yapar. TNF ile ilişkili apoptozu indükleyen ligand (TRAIL) ile indüklenen apoptozun DcR3 tarafından duyarlı hale getirildiği gösterilmiştir. DcR3'ün, hücre fonksiyonlarını kontrol eden "tuzak" ve "tuzak olmayan"" aktiviteleri olan bir "pleiotropik" çözünür faktör olduğu bulunmuştur. Fas ve FasL arasındaki bağlantı, bir IgG1 Fc alanı ile birleştirilmiş rekombinant DcR3 tarafından engellenebilir. TNF süper ailesi FasL, LIGHT ve TL1A üyelerini nötralize ederek apoptozu inhibe edebilir ve anjiyogenezi artırabilir. DcR3 serum seviyesi, enflamatuvar hastalıkları ve kanseri olmayan çoğu normal bireyde neredeyse saptanamaz düzeydedir. Birkaç araştırmaya göre, kandaki DcR3 seviyesi kanser hastalarında kanser evresi ile bağlantılıdır. Serum veya dokulardaki yüksek DcR3 seviyelerinin, bazı kanser hastalarında kötü prognoz ve/veya tedaviye direnç ile ilişkili olduğu bulunmuştur. Sonuç olarak, DcR3 serum seviyesinin eşik değerinin belirlenmesi, gelecekte hastalığın ciddiyetini tahmin ettirebilecektir. DcR3 ekspresyonunun inhibe edilmesi tümör büyümesini yavaşlatabilirken, DcR3 aracılı efektör fonksiyonların iyileştirilmesi, otoimmüniteyi azaltmak ve doku iyileşmesini desteklemek için uygun bir strateji olabilir. Bu nedenle, rekombinant DcR3 umut verici bir immünoterapi ajanıdır; yine de malign ortamda DcR3 ekspresyonunun önlenmesi kanser tedavisi başarısını artırabilir. Bu derlemenin amacı, şimdiye kadar DcR3 ile ilgili çalışmaların bulgularını toplayarak klinik kolaylık sağlamaktır. Bu keşifler kanser teşhisi, farklılaşma, metastaz ve evre tespiti konusunda yardımcı olabilir. Ayrıca, bunlar gelecekte karsinomları hedeflemek için yeni terapötik yaklaşımlar sağlayabilir.

Anahtar kelimeler: Biyobelirteç, DcR3, DcR3 ve kanser

Introduction

Decoy receptor 3 (DcR3/TNFRSF6B) is a receptor affiliated with the tumor necrosis factor receptor (TNFR) superfamily. Dissimilar to most members of the TNFR superfamily, the *DcR3* gene is not a cytoplasmic or transmembrane region, but encodes 300 amino acids with 29 residual signal sequences. The death ligament is

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a soluble receptor for three different TNF ligands (FasL, TL1A and LIGHT) that inactivate it by connecting to cd95L and is capable of neutralizing these ligands (1-5). The array resemblance between FasL, LIGHT, and TL1A is moderate (~30% identification) and each binds to different receptors eliciting different responses (5). There are studies showing that members of the TNFR superfamily can induce reverse signals after interacting with surface receptors (2).

The human *DcR3* gene is chromosomally mapped to 20q13.3 and this region is associated with many diseases (6). DcR3 mRNA is phrased in SW480 in lung tissues and colon adenocarcinoma (1). Recently, it has been reported that the C-terminal territory of DcR3, located except the TNF ligand-binding area, binds heparan sulfate proteoglycans (HSPGs) and triggers reverse signaling in antigen-presenting cells (APC) (5). There is a solid argument for overexposure of DcR3 in a variety of tumors such as lung, colon and pancreatic cancers, gastrointestinal tumors, malignant gliomas, virus-associated lymphomas, and tissues affected by autoimmune disease (7,8). Besides, excessive DcR3 expression was observed in cases of systemic lupus erythematosus or silicosis (9,10). DcR3 can act as a decoy or non-decoy receptor. In many cancer patients, DcR3 overexpression is associated with a worse prognosis of the disease. This proposes that excessive expression of DcR3 may breed some advantages for tumor growth and survival (2,6-8,11).

DcR3 and Its Functions

In their study, Yu et al. (1) used histidine-labeled recombinant DcR3 to scan soluble forms of TNF-ligand proteins with immunosuppressives. As a result, DcR3 was shown to bind especially to LIGHT and Fas ligand. While DcR3 prevents LIGHT-induced cytotoxicity in HT29 cells, LIGHT induces apoptosis of HT29 cells and various tumor cells. Data from the study showed that DcR3 suppressed LIGHT-mediated HT29 cell death by preventing the interaction of LIGHT with HVEM/TR2 and LTβR. It is therefore thought that DcR3, FasL and LIGHT may play a regulatory role in suppressing cell death (1).

Tang et al. (3) produced transgenic mice that over-expressed DcR3 in order to better understand DcR3's role in bone formation *in vivo*. Transgenic mice were compared with controls for bone mineral content (BMC) and total bone mineral density (BMD), resulting in much lower BMC and BMD in transgenic mice. After comparing DcR3 transgenic mice and control mice for BMD and BMC, there was a 35.7% reduction in trabecular bone volume in DcR3 transgenic mice. According to the study data, the number of osteoclasts incremented in DcR3 transgenic mice. However, regional administration of DcR3 to the tibial metaphysis significantly reduced the bone volume, BMC and BMD ratio of secondary spongiosis. Local injection of DcR3 has also been shown to increment the number of osteoclasts around the trabecular bone in the tibia. In an osteoclast activity experiment on substrate plates, it was stated that DcR3 remarkably incremented the absorption action of mature osteoclasts. High concentration DcR3 treatment slightly enhances nodule development and alkaline phosphatase action of primary cultured osteoblasts. From these results, it can be extracted that DcR3 induces the formation of osteoclasts from a bone stromal marrow cells, monocyte and, macrophage and this indicates that DcR3 may be critical in bone diseases and osteoporosis (3).

DcR3 is found in both rheumatoid arthritis (RA) and osteoarthritis (OA) fibroblast-like synoviocytes (FLS), according to the study by Hayashi et al. (12) DcR3-Fc protein inhibits Fas-source apoptosis in FLS, and DcR3 has been shown to increase down- regulation by siRNA and Fas-source apoptosis. In RA FLS, TNFa boosted DcR3 expression and prevented Fas-source apoptosis, but this was not the case in OA FLS (12).

To investigate autoimmune diseases, transgenic mice were generated by actin promoter-driven expression of human DcR3. While T-cell immune responses were suppressed in young DcR3-transgenic mice, the transgenic mice developed a systemic lupus erythematosus-like illness with distinct symptoms and produced autoantibodies against double helix DNA after 5-6 months. Proteinuria, leukocyturia, and hematuria were present in the kidneys, indicating accumulation of IgG, glomerular nephritis, and C3. Mice developed lymphocyte infiltration in their livers, skin lesions, as well as leukopenia, thrombocytopenia, anemia, similar to older transgenic mice. SLE-like syndrome was seen in approximately 60% of female transgenic mice versus 20% of males and was shown to be sex-related. Endogenous DcR3 and exogenous recombinant DcR3 (produced by transgenic T-cells) were shown to effectively protect T-cells against activation-induced apoptosis *in vitro*. Six months later, CD4 cells were increased in transgenic mice (13).

DcR3 makes cells of hematopoietic origin susceptible to TRAIL-induced apoptosis. DcR3 decreased host immunity by causing immune cell death, which You et al. (14) investigated. They showed that DcR3 induced dendritic cell (DC) apoptosis by activating PKC-δ and JNK to regulate DR5 upward by taking the Fas-related mortality area (FADD) to

spread apoptotic signals. The relationship of FADD with DR5 is that it activates the downstream apoptotic signaling cascade, causing the formation of the signaling complex (DISC) that leads to death. PKC-δ is activated (on DCs) by cross-linking heparan sulfate proteoglycan (HSPG) as the HBD. Fc fusion protein can trigger DC apoptosis. The results show the existence of a novel DcR3-mediated immunosuppressive mechanism (14).

Serum DcR3 levels in people with systemic lupus erythematosus were studied, and serum DcR3 levels in SLE patients were shown to be quite high. Also, when active SLE patients were compared with inactive SLE patients, the mean serum DcR3 level was found to be significantly higher in active patients. Soluble DcR3-Fc both reduced cell death induced by T-cells activated by FasL neutralization and, increased IL-2, T-cell proliferation and interferon-gamma production through co-stimulation of T-cells. In addition, lymphocytes taken from patients with SLE showed increased T-cell reactivity to common stimulation induced by DcR3, implying that elevated serum DcR3 was linked to heightened T-cell activation *in vivo*. The obtained information shows that serum DcR3 may be a guide in the pathogenesis of SLE (15).

Renal cell carcinoma tumor tissue samples and normal tissue samples from patients with renal cell carcinoma were compared for DcR3 expression. As a result of the study, high level of DcR3 expression was observed in renal cell carcinomas. Lymph node metastasis and the incision of distant metastasis were directly correlated with DcR3 expression, and metastases were found to be higher in the group with higher expression. DcR3 expression showed negative correlation with disease-specific survival ($p<0.001$) and non-progressive survival ($p<0.001$) in single-variable analyses. Patients with high-stage renal cell carcinoma expressing DcR3 had a 25% chance of 2-year survival, while patients with DcR3 negative tumors had a 65% chance of survival. DcR3 serum levels were also observed to be considerably greater in patients with advanced localized cancer and metastatic cancer (4).

Using human pancreatic cancer cells, high levels of DcR3 protein were shown in AsPC-1 cells through immunosuppression and ELISA method, while the presence of DcR3 in PANC-1 cells was not seen. Treatment with LY294002, wortmannin, Herbicide A, pyrrolidine dithiocarbamate or AG1024 has been shown to reduce endogenous DcR3 levels in AsPC-1 cells significantly. Also, transfection of AsPC-1 cells with IkappaBalpha or Akt dominant-negative plasmids lowered DcR3 levels considerably. DcR3 expression was enhanced in PANC-1 cells after a 48-hour transfection with a structurally active Akt (16).

The development of Crohn's disease is influenced by immune cell apoptosis resistance and epithelial barrier dysfunction. DcR3 neutralizes CD95L and thus displays an anti-apoptotic effect. The effect of DcR3 in Crohn's disease via CD95L was examined in one study. According to the results of the methods studied, DcR3 was found to be overexpressed in both actively inflamed and inactive regions of the epithelial layer of ileum samples in patients with Crohn's disease. People with Crohn's disease (active and inactive) had higher DcR3 expression levels compared to healthy people. TNF-α induces the expression of DcR3 in intestinal epithelial cells. The activation of nuclear factor kappa B (NF-kappaB) and the enhanced expression of DcR3 have been linked. As a result, it prevents CD95L-induced apoptosis in T-cells in the lamina propria and in intestinal epithelial cells. DcR3 can help with Crohn's disease inflammation by reducing CD95L-induced immune cell death and epithelial cell death and increasing NF-kappaB activation (17).

A study by Liang et al. (18) investigated the expression of survivin and DcR3 in colorectal carcinoma. Survivin mRNA and DcR3 mRNA levels in colorectal cancer tissues were shown to be greater than in surrounding tissues, according to RT-PCR data. Survivin protein and DcR3 protein expression levels in tumor tissues were considerably greater than levels in non-cancerous tissues according to western blotting data. In the immunohistochemical streptavidin-peroxidase (SP) method, DcR3 and survivin were positively correlated. They were more highly expressed in cancerous tissues (DcR3; 67.0% and survivin; 58.0%) compared to non-cancerous tissues (DcR3; 18.0% and survivin; 3.0%). According to the findings, DcR3 and survivin differentiation of colorectal cancer cells, as well as positive relationships with lymph node metastases and pathological stage, was found. DcR3 and survivin expression show a positive correlation with clinicopathological parameters of colorectal carcinoma (18).

The majority of follicles in mammalian ovaries experience atresia during the follicular development phase. Apoptotic cell death in granulosa cells is one of the features of this process. Fas ligand (FasL) and Fas, among other receptors and death bonds, were found in ovarian follicles, subsequently found to induce apoptosis in follicular cells. In light of this information, the expression of the default pig DcR3 mRNA in pig ovarian follicles was examined. The

nucleic acid sequence was found to have 80% homology compared to human DcR3, while the amino acid sequence was found to be 73% identical. According to the results of RT-PCR study, pDcR3 mRNA expression in granulosa cells from atretic follicles is weaker than in cells from healthy follicles. The individual layer cells, on the other hand, did not change significantly. While DcR3 regulates apoptosis in granulose cells during atresia, this is not the case in individual layer cells, according to these findings (19).

Yang et al. (20) investigated the concentration and clinical importance of DcR3 in serums of hepatocellular carcinoma (HCC) patients. According to the findings, serum DcR3 concentrations in patients with cirrhosis or HCC were considerably greater than in healthy people. Serum DcR3 levels in HCC patients were correlated with some factors such as TNM stage, metastasis, disease recurrence or para-cirrhosis. Protein expression and DcR3 serum levels had a positive connection in HCC tissues. Significantly elevated serum DcR3 levels, according to the findings, may have a role in the genesis, metastasis, and progression of HCC (20).

DcR3 was expressed in both osteoarthritis and normal chondrocytes in a study to investigate its roles on osteoarthritis chondrocytes. DcR3-Fc has been found to protect chondrocytes against apoptosis caused by Fas. DcR3-Fc boosted chondrocyte proliferation and selectively activated ERK phosphorylation. Chondrocyte proliferation induced by DcR3 is inhibited by blocking of the Fas-L antibody or pre-incubation of PD098059. DcR3 regulates chondrocyte proliferation in osteoarthritis chondrocytes via the ERK signaling pathway and Fas-source apoptosis (21).

The most prevalent kind of primary glomerulonephritis in the kidney is IgA nephropathy (IgAN), which affects mostly macrophages and T-cells. The theory that DcR3 can inhibit IgAN development, renal apoptosis, macrophage infiltration and T-cell activation was investigated in a study. A progressive IgAN (Prg-IgAN) model was used in mice with B cell deficiency. A short-term gene therapy was applied to mice with DcR3 plasmids through hydrodynamic-based gene transfer. When euthanasia was applied on the 21st day, compared to Prg-IgAN mice treated with empty vectors, they found systemic inhibition in T-cell proliferation and activation as a result of DcR3 gene therapy. Pro-inflammatory cytokines also have low serum levels. They found that progressive proteinuria, kidney function and kidney pathology decreased the rate of apoptosis in the kidney by suppressing macrophage and T-cell infiltration. DcR3 may be therapeutically beneficial in reducing IgAN development according to these data (22).

Yoo et al. (23) studied the expression of DcR3 in human endothelial cells and the effect of this expression in the early stages of Kaposi's sarcoma-associated herpes virus (KSHV). Infected cells were treated with recombinant human TL1A or anti-DcR3 antibody to assess cell proliferation and apoptosis. In the early stages of infection, DcR3 expression is upregulated. In the early phases of KSHV infection, DcR3 expression is critical for avoiding apoptosis in HUVECs, allowing for the effective formation and management of viral infection (23).

Pancreatic carcinomas and non-cancerous tissues were compared for DcR3 expression level, with the result that the ratio between tissues differed statistically significantly. DcR3 expression was shown to be associated with tumor size in the study. The preoperative pancreatic carcinoma resection group had a considerably higher level of DcR3 in their serum than the gallbladder carcinoma or benign pancreatic tumor groups. As a result, DcR3 is particularly effective in clinical-pathological factors in pancreatic carcinoma tissues that reflect tumor progression (24).

According to a study, DcR3 suppresses MHC II expression in TAMs via epigenetic regulation. Following this research, CT26-DcR3 stable transfects were developed to see if DcR3 promoted tumor growth. DcR3 transfections grew quicker than the vector control clone and led to TAM penetration. To evaluate tumor growth *in vivo*, CD68 promoter-guided DcR3 transgenic (Tg) mice were created. Macrophages from DcR3-Tg mice were compared with wild-type mice, resulting in higher levels of Ym1, arginase activity, IL-10, and IL-1ra, while MHC II, IL-12, IL-6, TNF-a, and NO were regulated downstream. A significant increase in tumor growth and spread was seen in DcR3-Tg mice. Tumor growth was eliminated with the histone deacetylase inhibitor sodium valproate and the arginase inhibitor N-ω-hydroxy-1-norargine. The results show that TAM activation is important for the effect of DcR3 in tumor development (6).

In the treatment of epithelial ovarian cancer, overcoming platinum resistance is a serious challenge. A study by Connor et al. (25) found that DcR3 was associated with platinum resistance. In a subsequent study, the effects of DcR3 on cellular interaction with epithelial ovarian cancer and platinum response were investigated. Women with epithelial ovarian cancer, who had high DcR3 levels in their peritoneal cavity, had a considerably shorter period until their first recurrence after platinum-based treatment. DcR3 is produced by non-malignant peritoneal cells. Despite not secreting DcR3, the cells investigated bind exogenous DcR3. This shows that cells can be affected by

DcR3 through external factors. All cells express CD44v3 and DcR3 binding heparan sulfate proteoglycans (HSPGs) Syndecans-2; however, DcR3s protein binding partners are poorly expressed or absent. Heparin and heparinase both block DcR3 binding. OVCAR-3 and SKOV-3 became more resistant to platinum (15% more) due to cell survival after exposure to DcR3, whereas CaOV3 became more vulnerable to platinum due to increased cell death (20-25%). According to the PCR results, BRCA1 mRNA expression increased in OVCAR-3 and SKOV-3 with DcR3 exposure, and BRCA1 expression decreased in CaOV-3. DcR3 easily binds to epithelial ovarian cancer cells through HSPGs and alters responses to platinum chemotherapy (25).

In one study, the DcR3 level was evaluated for early diagnosis of sepsis. A comparison was made by measuring the changes in plasma DcR3, IL-6, CRP and PCT levels of normal adults, SIRS and sepsis patients. As a result of the comparison, high DcR3 levels were observed in the majority of sepsis patients. For sepsis diagnosis, sensitivity was 97.69% and specificity was 98.04%. DcR3 density and sepsis level were positively correlated. In patients who died from sepsis, DcR3 levels increased in the blood culture 1-2 days before and reached the highest level on the 3rd day after blood culture was taken. In 13% of sepsis patients, PCT remained normal while DcR3 levels remained high. Based on these results, it is thought that DcR3 will assist in the follow-up of patients with sepsis (26).

According to a study conducted to understand the mechanism of DcR3 in gastric cancer, DcR3 increases migration, invasion, and proliferation and supports the epithelial-mesenchymal transition (EMT) of gastric cancer cells. It has also boosted the expression levels of DcR3, p-GSK-3β, β-catenin, GSK-3β and p-AKT, which are all components of the β-catenin/AKT/PI3K/GSK-3β signaling pathway. It also boosted vimentin and N-cadherin expression while decreasing E-cadherin expression. These findings showed that DcR3 played an important role in invasion of β-catenin/AKT/PI3K/GSK-3β and cell proliferation during gastric cancer progression. As a result, DcR3 is considered to be at an important point for the treatment of gastric cancer (27).

A study by Wei et al. (28) examined the function of DcR3 in liver cancer. As a result of the research, they found that DcR3 was regulated upwards in liver cancer tissues and serum. High levels of DcR3 were linked to aggressive clinicopathological features and a bad prognosis. While DcR3 increased invasion and cell migration *in vitro*, it directed tumor growth *in vitro* and *in vivo*. Furthermore, DcR3 resulted in a significant upregulation of interferon regulatory factor 1 (IRF1). In addition, DcR3 also supported cell adhesion molecule 1 (CEACAM1) expression associated with carcinoembryonic antigen through activated IRF1. The findings add to our understanding of DcR3's function and mechanism in liver cancer etiology (28).

In a study, DcR3 expression was suppressed in HepG2 cells to examine the effect of FasL on liver cancer HepG2 cells. In the investigation, FasL (10 ng/mL) was utilized to treat wild-type HepG2 cells (WT), DcR3 empty plasmid control HepG2 cells, and DcR3 siRNA knockout HepG2 cells (KD). After the treatment, when the WT cells in the G2/M phase were compared with the KD cells, it was seen that the KD cells decreased. FasL-induced apoptosis was more likely in KD cells. While the activity and migration of KD cells decreased with treatment, the expression of MMP9, VEGF-D, and VEGF-C also decreased. DcR3 was also implicated in the invasion and proliferation of HepG2 cells, a mechanism that could be linked to the regulatory influence of VEGF-D, VEGF-C, and MMP9 expression. Following DcR3 knockdown, FasL-mediated apoptosis was enhanced in HepG2 cells. As a result, FasL-coupled DcR3 may offer hope for treatment in liver cancer (29).

In a study by Zhu et al. (30), the relationship between hepatocellular carcinoma and DcR3 was examined. In this study, the TGFβ3-Smad-Sp1 signaling pathway was discovered to be responsible for the overexpression of DcR3 in hepatocellular carcinoma. DcR3 overexpression was associated with tumor invasion and metastasis in hepatocellular carcinoma tissues. While DcR3 inhibited the secretion and differentiation of Th1 cells, it significantly promoted the secretion and differentiation and of Th2 and Treg cells. In contrast, knocking down DcR3 expression in hepatocellular carcinoma dramatically improved CD4+ T-cell immunity. Finally, inhibiting DcR3 expression may provide a new immunotherapeutic treatment for HCC patients (30).

In one study, DcR3 was silenced to examine the susceptibility of HCC cells to TRAIL. In comparison to the LO-2, DcR3 was strongly expressed in Huh-7, HepG2, Hep3B, BEL-7402, SMCC7721, and MHCC97H cell lines. BEL-7402 and HepG2 were found to be tolerant to TRAIL-mediated apoptosis, which negatively correlated with DcR3 expression. In HepG2 and BEL-7402, shRNA-mediated silencing of DcR3 and treatment with TRAIL resulted in severe apoptosis, whereas more cancer cells were identified in the G1 phase. SiDcR3 can activate caspase-8, -9, and -3 when paired with TRAIL, increasing the expression of the protein Bax

while reducing the expression of non-apoptotic proteins. According to the findings, decreased concentration of DcR3 may promote apoptosis via TRAIL in hepatocellular carcinoma (31).

In another study, individuals with various malignancies and healthy individuals were evaluated in terms of DcR3 serum levels. Patients with breast cancer, lymphoma, and stomach malignancies had considerably greater DcR3 levels in their serum. DcR3 was also found to be linked with platelet distribution width (PDW) in metastatic malignancies. Based on this result, serum DcR3 together with hematocrit (Hct), hemoglobin (Hb) and PDW may be helpful in tracking the formation of cancer metastases. According to the findings, DcR3 can be used in early diagnosis for gastric cancer detection and metastasis when evaluated with hematological features (32).

In a study by Safaya et al. (33), DcR3 levels were examined in sickle cell anemia. Peripheral blood mononuclear cells (PBMC) were extracted from the blood of healthy controls and sickle cell anemia patients for research purposes. For real-time (RT) gene expression of DcR3/DR3/TL1A, RNA extracted from PBMC was employed. Within SCA patients with alpha-globin gene deletions or co-hereditary fetal Hb (HbF), gene expression was examined in subgroups. According to the study, they found that DcR3 and TL1A expression increased, while DR3 expression decreased in PBMC of sickle cell anemia subjects compared to normal control PBMC. While TL1A/DcR3 expression was lower in sickle cell anemia subjects with HbF>10%, DcR3/TL1A expression was higher in subjects with HbF<10%. Furthermore, patients with HbF greater than 10% had considerably fewer pain episodes than those with HbF less than 10%. The levels of DR3, DcR3 and TL1A circulating in the plasma of sickle cell anemia patients were found to be considerably higher. HbF above 10% moderates TL1A elevation, while HbF below 10% exacerbates TL1A/DcR3 reactions. Based on the findings, it is possible that increased DcR3 and TL1A expression in sickle cell anemia participants' PBMC during painful vasoocclusive crisis contributes to the pathogenesis of vasoocclusive crisis in sickle cell anemia with altered TL1A expression (33).

A study was conducted by Yang et al. (34) to examine the anticancer effects of triptolidine (TPL) on DcR3 in preclinical patient-derived tumor xenograft (PDTX) models of oral squamous cell carcinoma. The effects of TPL on cell proliferation and DcR3 expression in PDTX models and oral squamous cell carcinoma cell lines were examined as part of the study. Excess TPL therapy dramatically slowed tumor growth, while DcR3 expression was related to tumor size and survival. In *in vitro*, *in vivo*, and in PDTX models, TPL inhibited the synthesis of metastasis-associated protein 1 (MTA1), a transcription factor for DcR3. As a result, TPL was demonstrated to have anticancer properties in *in vitro*, *in vivo*, and in PDTX models via inhibiting DcR3 and MTA1 (34).

In a study by Zhang et al. (35), DcR3 levels were investigated in patients with lung cancer. For the study, DcR3 protein expression in normal lung tissues and lung cancer was compared. In addition, using the Cancer Genome Atlas database, the diagnostic and clinicopathological significance of DcR3 mRNA in lung cancer patients was investigated. DcR3 expression was found to be quite high in lung cancer tissues. In comparison to normal lung tissues, DcR3 was overexpressed in adenocarcinoma tissues and squamous cell carcinoma. In addition, DcR3 expression was found to correlate with tumor stage, tumor diameter, overall survival of lung adenocarcinoma and disease-free survival (35).

A study investigated the impact of tumor necrosis factor-derived protein-8 (TIPE) on DcR3 expression in colorectal cancer. TIPE and DcR3 were both highly expressed in colorectal cancer patients, and their levels were also positively associated. DcR3 and TIPE expression in HCT116 cells was verified to be high. TIPE overexpression boosted the DcR3 promoter's transcriptional activity. In conclusion, in addition to being significantly expressed in DcR3 and TIPE colorectal cancer, they are associated with a poor prognosis. TIPE regulates DcR3 expression and reduces apoptosis in colorectal cancer cells by stimulating the AKT/PI3K signaling pathway (36).

In another study, serum DcR3 levels were evaluated in 85 bronchial asthma patients. According to the results, serum DcR3 levels of asthmatic patients were found to be higher than those of healthy controls. Serum DcR3 levels were found to be inversely linked to the asthma control test score in patients with atopic asthma. DcR3 has the feature of being a good biomarker for atopic asthma, especially in children (37).

One study compared *in vivo* and *in vitro* studies to investigate DcR3 levels in kidney disease. Elevated serum DcR3 correlated positively with inflammatory indicators such as IL-6, adhesion molecules and high-sensitivity C-reactive protein in maintenance hemodialysis (HD) patients. DcR3 expression was originally thought to be connected to a 2-fold increase in blood creatinine or kidney

allograft failure. DcR3 protects renal myofibroblasts from Fas-induced apoptosis and causes renal fibrosis as a result. DcR3, which is expressed locally in renal tubular epithelial cells (RTECs), has been shown to decrease FasL-Fas-mediated T-cell apoptosis and produce an increase in allo-reactive T-cells. Cytomegalovirus promoter-driven human DcR3 plasmid and recombinant DcR3.Fc have been found to affect the activation and differentiation of dendritic cells and macrophages by ''non-decoy'' activity in addition to traditional biological roles. After hydrodynamic-based gene delivery of the DcR3 plasmid, both autoimmune crescentic glomerulonephritis and progressive IgA nephropathy in mice can be inhibited. *In vitro* study of overexpressing DcR3 or adding recombinant DcR3.Fc can be utilized to evaluate DcR3-mediated effects, whereas systemic effects *in vivo* can be investigated using CD68-driven DcR3 transgenic mice. Inhibiting DcR3 expression in humans could be a promising way to investigate pathogenic mechanisms (38).

HCC has been linked to chronic hepatitis B (CHB). DcR3 expression was investigated during hepatitis B virus (HBV) infection by Liang et al. (39). The researchers discovered that DcR3 was overexpressed in CHB patients, DcR3 overexpression was linked to HBV DNA burden and liver injury. They discovered that hepatitis B virus X protein (HBx) increased DcR3 expression, but that NF-kB inhibitors inhibited this rise. By attaching NF-kB subunits to the p65 and p50 DcR3 promoters, HBx also activated NF-kB and elevated DcR3. PI3K inhibition reduced DcR3 expression and prevented NF-kB from binding to DcR3 promoters. According to the findings, HBx stimulates DcR3 expression via the NF-kB/PI3K pathway. This pathway was assumed to play a role in the progression of HBV-mediated hepatocellular carcinoma (39).

In a study, DcR3 expression level and clinical significance were investigated in patients with acute chronic liver failure. The levels of serum DcR3 in individuals with acute chronic liver failure and patients with chronic liver disease who did not have acute failure were compared. Acute chronic liver failure patients have considerably greater serum DcR3 levels than non-acute chronic liver failure patients. International standardized ratio, aspartate aminotransferase, and prothrombin time were all favorably connected with neutrophilic granulocytes, while serum albumin and platelets were negatively correlated. While DcR3 level in the early stage of acute chronic liver failure disease did not differ much between survivors and non-survivors, DcR3 level increased in the late stage non-survivor group and gradually decreased in the survivor group. The findings imply that DcR3 may play a significant role in the prognosis of acute chronic liver failure patients (40).

Endometriosis is a multifactorial inflammatory illness in which the nuclear factor-κB (NF-κB) signaling pathway is persistently activated. The aberrant adherence of the endometrium is the first step in the evolution of endometriosis. DcR3 appears to be able to increase cell adhesion via activating focal adhesion kinase. They discovered that activation of the Akt-NF-κB signaling pathway elevated DcR3 in human ectopic endometrial cells, and that its expression was positively linked with intercellular adhesion molecule 1 (ICAM-1) and target cell adhesion molecule (HCAM; CD44). Knockdown of DcR3 reduced HCAM and ICAM-1 expression and also reduced cell migration and adhesion. The finginds support that DcR3 plays an important role in the pathophysiology of endometriosis and suggest that inhibiting DcR3 expression could be a promising therapy option for endometriosis (41).

Serum DcR3 level is elevated in chronic inflammatory diseases. In one study, IL-6 and DcR3 levels were measured in chronic obstructive pulmonary disease (COPD) patients and control subjects, and then correlation with airflow limitation by COPD stage was evaluated. The patient group consisted of patients with stable COPD (SCOD) and acute COPD exacerbation (AECOPD). Both IL-6 and DcR3 levels were increased ($p<0.01$ to 0.001), positively correlated with increased airflow limitation in the AECOPD and SCOPD groups. In addition, DcR3 and IL-6 levels were positively correlated with smoking history (annual). The serum DcR3 level rose with the severity of the increasing airway limitation, particularly during the acute exacerbation period in male COPD patients, according to the findings. These findings imply that DcR3 is linked to the underlying pathophysiology of COPD in male (42).

In a study, the mechanism of DcR3 in osteoclastogenesis induced by interleukin-1α (IL-1α) was investigated. IL-1α is a potent cytokine involved in bone loss and inflammatory arthritis. Considering the results, DcR3 inhibited bone resorption and suppressed IL-1α-induced osteoclastogenesis in RAW264.7 cells and primary murine bone marrow-derived macrophages (BMM). Expressing DcR3, IL-1a, secretory IL-1ra (sIL-1ra), intracellular IL-1ra (icIL-1ra), reactive oxygen species (ROS) and activating interleukin-1 receptor-associated kinase 4 (IRAK4) induced osteoclast precursor cells treated with RANKL. The abundance of buildup of ROS, expression of Fas ligand and IL-1ra secretion in apoptotic osteoclast precursor cells are

hypothesized to be responsible for the inhibition of DcR3 during IL-1 or RANKL induced osteoclastogenesis. It was discovered that DcR3 inhibited osteoclastogenesis through increasing ROS levels and the expression of ROS-induced Fas ligands, IL-1ra and IL-1a. According to the findings, increased DcR3 in preosteoclasts could be a viable target for therapy in inflammatory IL-1-induced bone resorption (43).

In the study by Chang et al. (44), the role of DcR3 in lung cancer was investigated. Within the scope of the research, DcR3 expression was examined in 461 lung adenocarcinomas. DcR3 was more expressed in acinar patterns, micropapillary, solid, as well as tumors with wild-type EGFR status, according to the findings. Furthermore, the disease-free survival rate for stage I patients was shown to be lower, which was linked to DcR3 expression level. Lung cancer differentiation and development are hypothesized to be influenced by DcR3 expression. DcR3 is also useful in the clinical setting of tumor growth for stage I in lung adenocarcinoma (44).

The effect of DcR3 on breast cancer prognosis was examined by Ge et al. (45). The study investigated the expression of DcR3 in MDA-MB-231 and MCF7 cell lines and used 115 breast tissue samples. While evaluating the results, patient groups were formed as those with good and with bad prognosis. When DcR3 expression in the patient groups was evaluated, the expression level in the bad prognosis group was found to be considerably higher than in the good prognosis group. DcR3 transcripts in stage 2 cancers, compared to stage 1 cancers, were found to increase significantly. DcR3 improves the ability of breast cancer cells to invade and plays a significant role in breast cancer metastasis according to the findings (45).

A study looked into the clinical implications of DcR3 overexpression in people with hepatic fibrosis and chronic hepatitis B. The study comprised 128 participants who had been clinically diagnosed with chronic hepatitis B and had their livers biopsied. The levels of DcR3, type III procollagen, hyaluronic acid (HA), laminin protein, and type IV collagen (IV-C), expression were all measured. DcR3 levels were observed to be considerably greater in chronic hepatitis B patients (especially in active disease). Patients with liver fibrosis and chronic hepatitis B with liver cirrhosis had higher DcR3 expression than patients with chronic hepatitis B without liver fibrosis. DcR3 is a marker for liver fibrosis in people with hepatitis B infection according to the findings. The use of DcR3 in conjunction with HA and IV-C may enhance the diagnostic value of DcR3 in the diagnosis of liver fibrosis (46).

Chen et al. (47) examined serum DcR3 levels in patients with atopic and non-atopic asthma. The serum DcR3 levels of asthmatics and healthy people were compared as part of the study. According to the presence or lack of allergen-specific immunoglobulin E (IgE), asthma patients were categorized into two subgroups: Non-atopic and atopic. In asthma patients, the average serum DcR3 level was considerably greater than in healthy controls. There was no noticeable difference in DcR3 levels between atopy patients and those who did not have atopy. However, total eosinophil count was favorably linked with serum DcR3 level. DcR3 blood levels were associated with illness severity in non-atopic asthma patients, suggesting that DcR3 could be a feasible biomarker for predicting non-atopic asthma severity (47).

In a study, DcR3 levels were examined in patients with severe burns. Within the scope of the study, the patient group (n=10) with severe burns was followed up in terms of PCT, DcR3, IL6, CRP, SOFA score, thrombocyte and white blood cell (WBC). DcR3 level increased on the first day. DcR3 levels were comparatively low in survivors, but they were consistently high in non-survivors. Continuously increasing DcR3 levels were observed in three patients, and these patients subsequently died. In the other two patients who did not survive, the DcR3 level peaked and decreased before death. A good correlation was observed between DcR3 and PCT, while DcR3 showed less correlation with platelet, CRP, WBC, SOFA score and IL6. DcR3 levels were discovered to be a valuable biomarker for understanding the clinical severity of severe burns and monitoring a mortality prediction as a result of the research (48).

Bou-Dargham et al. (49) conducted research on the mechanisms of immune avoidance (IEM) in prostate cancer. IEMs are used in various combinations in prostate cancers. Increased DcR3, cytotoxic T lymphocyte-associated protein 4 (CTLA4) and immunological ignorance were found in the majority of prostate cancer patients (51.6%). Some of the immunologically deficient patients had increased DcR3 expression, some up-regulated CTLA4, and some had all three pathways up-regulated. These data show that most human prostate cancer specimens are immunologically cold tumors that are resistant to mono-immunotherapy. These biomarkers can better understand a patient's immune-avoidance processes so that definitive treatment plans can be created to increase therapeutic efficacy (49).

In a study, it was investigated whether DcR3 and tumor necrosis factor (TNF)-like cytokine 1A (TL1A) played a role in promoting atherosclerosis. Plasma TL1A and DcR3 levels were compared in patients without coronary artery

disease and in patients with coronary artery disease who underwent coronary artery bypass grafting. The relationship between SYNTAX and coronary artery disease scores was also investigated. The coronary artery disease group had considerably greater plasma levels of DcR3 and TL1A than the non-coronary artery disease group. TL1A and DcR3 were found to be substantially linked with the existence of coronary artery disease in multivariate analysis. Furthermore, in coronary artery disease patients, TL1A was found to be positively and strongly linked with the SYNTAX score. Both DcR3 and TL1A levels are higher in coronary artery disease patients who require coronary artery bypass grafting, suggesting that they could be valuable biomarkers for detecting severe coronary artery disease. Furthermore, TL1A levels are related to the SYNTAX score, suggesting that it could be employed as a coronary artery disease severity indicator (50).

One study evaluated the levels of DcR3 in the blood of people who had coronary heart disease. In C57BL/6 mice with coronary heart disease, the effects of DcR3 on apoptosis and inflammation were investigated. In mice with coronary heart disease, DcR3 plasma concentrations were observed to be reduced. When DcR3 injection was given to mice with coronary heart disease, it was seen that the symptoms of the disease were reduced, while it was seen that it increased survival time by reducing inflammatory responses and myocardial cell death. DcR3 concentrations in the blood can be used to predict the risk and prognosis of the disease. DcR3 has also been shown to regulate the protein kinase B (AKT)/PI3K signaling pathway, which limits the production of inflammatory factors. The amount of DcR3 in circulation seems to be linked to the severity of the condition. The modulation of DcR3 in the AKT/PI3K signaling pathway has been suggested as a potential treatment for coronary heart disease (51).

The goal of one study was to use immune-related gene expression to classify different forms of breast cancer. Bou-Dargham et al. (49) identified 7 clusters on the Cancer Genome Atlas RNA-seq breast cancer data using the sequential binary clustering method. They found that 34.3% of the deaths were caused by Programmed cell death-1 (PD-1). DcR3 and TGF-β have been identified as new therapeutic targets for the treatment of breast cancer. Because 57.7% of patients overexpress TGF-β and DcR3, targeting these two molecules could be a powerful technique for breast cancer treatment. It was also observed that triple-negative breast cancer (TNBC) patients were equally clustered into two subgroups. The first had a problem with antigen presentation, whereas the second had four separate hijacking mechanisms as well as a high leukocyte uptake. As a result, various immunotherapy techniques can be used to treat different TNBC patients. These findings aid researchers in better understanding how patients respond to immunotherapies and shed information on the rational development of new combination treatments (52).

Gout is an inflammatory disease caused by the accumulation of monosodium urate (MSU) crystals in the joints. It stimulates macrophages to a proinflammatory state and induces neutrophil recruitment by triggering NLRP3-dependent production of interleukin-1β (IL-1β). DcR3 and its non-decoy action motif, the heparin sulfate proteoglycan (HSPG) binding domain (HBD), were studied in macrophages and mice to see how they affected MSU crystal-induced NLRP3 inflammatory activation. Both HBD.Fc and DcR3.Fc inhibited MSU crystal-induced IL-1β secretion and NLRP3 activation in THP-1, U937 cells, and bone marrow-derived macrophages, according to the findings. In DcR3-transgenic mice expressing DcR3 in myeloid cells, MSU was found to cause less IL-1β and chemokine release, an enhanced M2/M1 macrophage ratio, and reduced neutrophil recruitment in the air sac mouse model of gout. In addition, less inflammatory response was observed in mice treated intravenously with HBD.Fc or DcR3.Fc. The data show that by modulating lysosomal and mitochondrial processes, HBD of DcR3 can attenuate MSU crystal-induced NLRP3 inflammatory activation (53).

It was investigated if DcR3 might ameliorate neuroinflammation and Alzheimer's disease-like impairments in the central nervous system based on its immunosuppressive effect in a study. Human APP transgenic mice (J20 line) were crossed with human DcR3 transgenic mice to generate DcR3, APP, APP/DcR3 and wild-type mice for analysis. As a result of the study, it was observed that DcR3 reduced amyloid plaque accumulation and ameliorated hippocampus-related memory deficits in APP transgenic mice. DcR3's protective mechanism interacts with heparan sulfate proteoglycans and activates IL-4^{+}YM1^{+} M2a-like microglia, reducing Aβ-induced proinflammatory cytokines and enhancing microglia's phagocytosis capabilities. According to the findings, upregulation of DcR3 expression in the brain could be a viable treatment method for Alzheimer's disease (54).

The MAPK kinase/mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK)

signaling pathway controls DcR3 expression. In 30 patients with stage III gastric adenocarcinoma, researchers looked for expression of TIPE (α-induced protein 8), DcR3 and ERK in normal gastric tissues and pathological tissues. DcR3, TYPE and ERK1/2 expression in tumor tissues was significantly increased when tumor tissues of gastric cancer were compared with paracarcinoma tissues. However, TIPE expression was positively correlated with ERK1and DcR3 levels. Based on the findings, TIPE can be linked to the expression of ERK1/2 and DcR3, which may be implicated in gactric cancer cell death, and could be considered as a new biomarker for gastric cancer (55).

In one study, the cellularity of the downregulated sample of DcR3 in the cholangiocarcinoma cell line TFK-1 was examined on cell apoptosis and cell uptake. For this study, three distinct cell lines were grown. For investigation, the cholangiocarcinoma cell line with the greatest DcR3 expression was chosen. Expression of DcR3 was silenced in the selected cell line by transfection with DcR3-siRNA. Various biological phenotypic parameters, including cell cycle, cell viability and apoptosis, were found. TFK-1 was selected by measuring the protein levels and mRNA of DcR3 in three cell lines. After 48 hours of treatment with DcR3-siRNA, DcR3 mRNA, G0/G1 ratio increased and the G2/M ratio decreased in the treatment group. These findings point to the necessity for more research into the molecular mechanisms that regulate DcR3 expression in cholangiocarcinoma (56).

Conclusion

DcR3's potential in cancer, particularly as an anti-tumor target, is yet unknown. In summary and importantly, the differential expression and function of DcR3 has been highly implicated in cancer studies. DcR3 is associated with several ligands capable of influencing apoptosis, angiogenesis, and immune escape of tumors. DcR3 can both be considered a positive and negative regulator during cancer development and progression according to research. While increasing DcR3 expression is beneficial for the treatment of inflammatory diseases and enhances tissue repair, inhibiting DcR3 expression increases tumor apoptosis and suppresses tumor growth *in vivo*. Based on these findings, DcR3 can now be regarded a possible target for cancer gene therapy as well as an anticipating marker for malignant tumors.

Ethics

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Drafting Manuscript: N.H., H.G.Ç., A.K., Critical Revisation of Manuscript: N.H., H.G.Ç., A.K., Final Approval and Accountability: N.H., H.G.Ç., A.K.

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