

## Decoy receptor 3: Its role as biomarker for chronic inflammatory diseases

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### Abstract

Members of the tumor-necrosis factor- $\alpha$  (TNF- $\alpha$ ) and TNF- $\alpha$  receptor (TNFR) superfamilies of proteins (TNFSF and TNFRSF, respectively) play important roles in the function of the immune system. Decoy receptor 3 (DcR3, TNFRSF6b) is a decoy receptor that binds to three TNFSF ligands, FasL, LIGHT and TL1A. Association to these ligands competes with the corresponding functional receptors and blocks downstream signaling, leading to immunomodulatory effects, including the prevention of apoptosis. DcR3 lacks a transmembrane region and exists only as a secreted protein, which is detectable in biological fluids. Recent studies have shown that DcR3 is upregulated and may be pathogenetically implicated in several and diverse chronic inflammatory diseases. The strongest associations have been described for rheumatological diseases, mainly systemic lupus erythematosus and rheumatoid arthritis, inflammatory bowel disease, and serious infectious conditions, including systemic inflammatory response syndrome. In the majority of these conditions, DcR3 mRNA and protein expression is elevated both at the target tissues as well as in the systemic circulation. DcR3 concentration in the serum is untraceable in the majority of healthy individuals but can be detected in patients with various inflammatory diseases. In most

such cases, soluble DcR3 correlates with disease severity, as patients with severe forms of disease have significantly higher levels than patients with milder or no activity. In addition, effective anti-inflammatory treatment leads to the disappearance of soluble DcR3 from the circulation. Taken together, current evidence suggests that serum DcR3 may become a useful biomarker for chronic inflammatory disorders, as it is up-regulated in response to inflammatory stimuli, and may serve both as a prognostic marker for disease severity and as a surrogate indicator of response to treatment.

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**Key words:** Decoy receptor 3; Tumor necrosis factor receptor superfamily of proteins; Chronic inflammation; Infection; Disease activity; Biomarker

**Core tip:** Members of the tumor-necrosis factor- $\alpha$  (TNF- $\alpha$ ) and TNF- $\alpha$  receptor superfamilies play important roles in the function of the immune system. Decoy receptor 3 (DcR3) is a decoy receptor that exists only as soluble protein and has the ability to bind to FasL, LIGHT and TL1A. Recent studies showed that DcR3 is upregulated and may be pathogenetically implicated in systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease and infection. DcR3 may become a useful biomarker for chronic inflammatory disorders, as it is upregulated in response to inflammatory stimuli, and may serve both as a prognostic factor for disease severity and as an indicator of response to treatment.

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## INTRODUCTION

Decoy receptor 3 (DcR3, alternative names TR6 or M68) is a member of the tumor necrosis factor receptor superfamily (TNFRSF), officially designated TNFRSF6b<sup>[1]</sup>. It forms part of a distinct subset within the family of TNFR-like proteins, namely the decoy receptor family, which also includes DcR1, DcR2 and osteoprotegerin<sup>[2]</sup>. DcR3 shares a very similar protein sequence identity with osteoprotegerin in that they both lack a transmembrane region; hence, they exist solely in a secreted form as soluble receptors<sup>[3]</sup>.

It should be mentioned that the original publications for DcR3/TR6/M68 reported high expression of this protein in a variety of neoplastic tissues. This, in combination to its anti-apoptotic function that is described below led to a large body of research regarding the importance of this cytokine in carcinogenesis. The present review will focus exclusively to the recently appreciated role of DcR3 as an immunological-mediator and inflammatory biomarker. In particular, the association with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and infection will be presented in detail.

## REGULATION OF DcR3 EXPRESSION

The *tnfrsf6b* gene that encodes for the human DcR3 protein is located at chromosome 20 (20q13.3). The translational product is a protein containing 300 amino acids<sup>[4]</sup>. Western blot analysis of samples from transgenic mice for the full-length human DcR3 estimated a molecular size of 33 kDa and evidence for a glycosylated protein<sup>[4]</sup>. DcR3 is not found in mouse or rat genomes; on the other hand, sequences homologous to the *tnfrsf6b* gene have been described in a variety of species such as chicken, frog, chimpanzee or cattle<sup>[5,5]</sup>.

DcR3 mRNA is detected in variable amounts in healthy adult tissues, including spleen, colon, lung, stomach, spinal cord, lymph node, and trachea<sup>[1,4,6]</sup>. In contrast, its expression is weak in the thymus and undetectable in peripheral blood lymphocytes<sup>[1]</sup>. In addition, immunoreactivity against DcR3 protein was usually weak or undetectable in normal tissues, with the exception of the luminal portions of crypt epithelium<sup>[4]</sup>. At the cellular level, DcR3 transcripts were present, although weakly, in most hematopoietic cell lines and induced upon activation in Jurkat T leukemia cells. Finally, DcR3 mRNA were constitutively and strongly expressed in the endothelial cell line, HUVEC<sup>[6]</sup>.

The regulation of DcR3 expression is not fully elucidated and reported results may differ between different cell-types or between different experimental systems (Figure 1). *In vitro* studies in intestinal epithelial cells show elevated expression of DcR3 mRNA after stimulation with lipopolysaccharide or tumor-necrosis factor- $\alpha$  (TNF- $\alpha$ )<sup>[7,8]</sup>. LPS-induced DcR3 upregulation in IECs is mediated through the activation of extracellular signal-

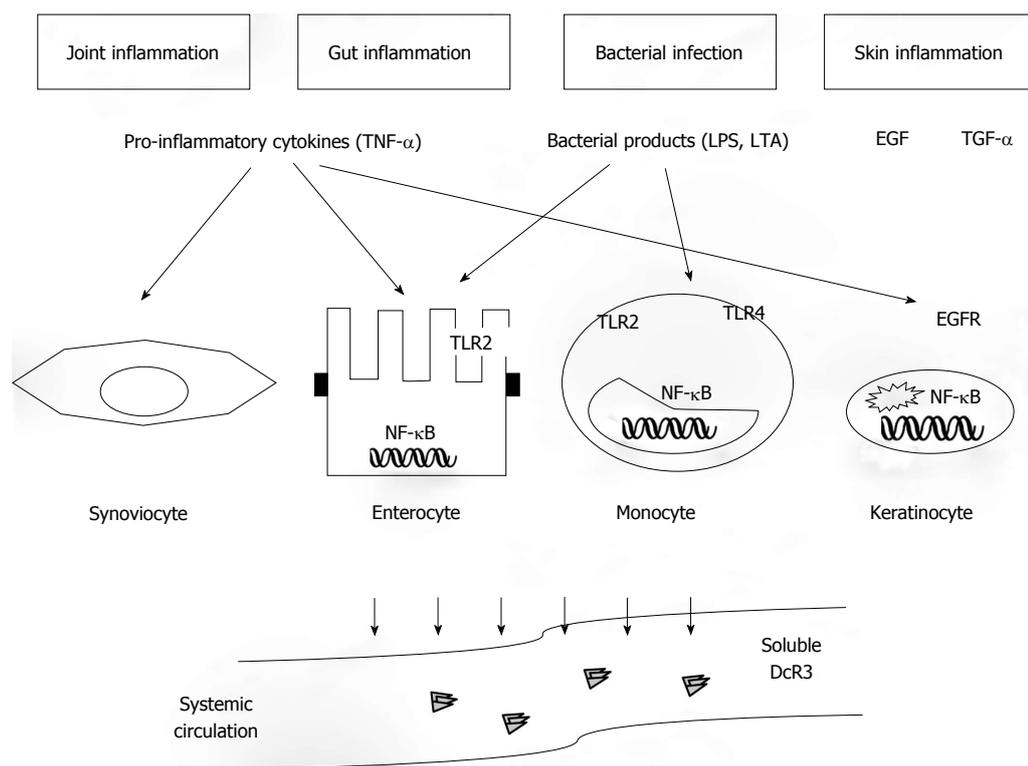
regulated kinase 1 and 2 and c-Jun NH2-terminal protein kinase, as well as of the transcription factor NF- $\kappa$ B. In human monocytes and myeloid-derived dendritic cells, DcR3 secretion was induced *via* Toll-like receptors -2 and -4<sup>[9]</sup>. This was dependent upon the p42/p44 mitogen-activated protein kinases, Src-like protein tyrosine kinases, and phosphatidylinositol 3-kinase. Finally, in keratinocytes, DcR3 mRNA expression is downregulated after exposure to UVB irradiation<sup>[10,11]</sup>.

## FUNCTION OF DcR3

The soluble DcR3 protein is capable of binding to three ligands of the tumor necrosis factor superfamily (TNFSF), in particular, Fas ligand (FasL/CD95L/TNFSF6)<sup>[1]</sup>, lymphotoxin-like inducible protein that competes with glycoprotein D for herpesvirus entry on T cells (LIGHT)<sup>[6]</sup> and TNF-like molecule 1A (TL1A)<sup>[12]</sup>. All TNFSF members are type II transmembrane proteins. They are initially expressed as membrane-bound molecules but subsequently may be cleaved off from the membrane and released in the peripheral circulation. It should be noted that, both membrane-bound and soluble forms of these ligands are functional<sup>[13]</sup>. The three ligands that recognize DcR3 are also capable of binding to additional TNFRSF members that act as the functional (as opposed to decoy) receptors. In particular, FasL binds to Fas<sup>[1]</sup>, LIGHT to lymphotoxin-beta receptor and to the herpesvirus entry mediator (HVEM)<sup>[14]</sup>, and TL1A to Death Receptor 3 (DR3)<sup>[12]</sup>. DcR3 competes for ligand binding, restricting therefore functional signaling mediated by Fas/FasL, LIGHT/HVEM, and TL1A/DR3 interactions. As a result, the functional importance of DcR3 has been associated with two pathways, primarily: first as an anti-apoptotic protein and second as an immunomodulatory molecule<sup>[15]</sup>. It should be noted that the lack of DcR3 expression in the mouse is associated with difficulties in the study of its function, as it prohibits mechanistic studies in knockout strains or pharmacological neutralization of the molecule.

Several studies have clearly shown that DcR3 inhibits apoptosis. This is accomplished through its ability to prevent functional association between TL1A/DR3, FasL/Fas, and LIGHT/HVEM, which all lead to programmed cell death<sup>[1,6,12]</sup>. Although DcR3-mediated regulation of cell death has been primarily emphasized for neoplastic conditions, it also has relevance to the pathogenesis of immunological responses as well. Indeed, inhibition of apoptosis of leukocytes may lead to perpetuation of chronic tissue injury<sup>[16]</sup>. Such a mechanism is of great importance, as effector lymphocytes are a critical cellular component of most chronic inflammatory conditions<sup>[17]</sup>.

In addition to inhibiting apoptosis, DcR3 exerts additional immunomodulatory functions as well. Many of these are also mediated through blockade of interactions between its ligands (FasL, LIGHT, TL1A) and their respective functional receptors (Fas, HVEM, DR3), as immunostimulatory signaling is also generated through the latter.



**Figure 1 Upregulation of Decoy receptor 3 in chronic inflammation.** Decoy receptor 3 (DcR3) exists solely as a secreted protein, which becomes detectable at the peripheral blood of patients with a variety of inflammatory conditions. The most stable associations have been described for gut and joint inflammation as well as for infectious diseases. DcR3 upregulation is mediated via diverse inflammatory stimuli, including pro-inflammatory cytokines [most prominently tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )], bacterial-derived factors such as lipopolysaccharide (LPS) or lipoteichoic acid (LTA), and growth factors including epidermal growth factor and transforming growth factor- $\alpha$ , which interact with their respective receptors. Regulation is highly dependent upon the target cell population, although there is considerable overlap between the various targets. In monocytes and small intestinal epithelial cells LTA and LPS interact with TLR-2 and -4, whereas TNF $\alpha$  is a potent stimulator of DcR3 expression in various cell populations, including epithelial cells and keratinocytes. Nonetheless, a common final signalling pathway for DcR3 induction appears to be the activation of the transcription factor NF- $\kappa$ B. The latter is a final step that leads to the transcriptional activation of the *tnfrsf6b* gene and release of the DcR3 protein into the systemic circulation. EGF: Epidermal growth factor; TGF- $\alpha$ : Transforming growth factor- $\alpha$ ; TLR: Toll like receptor; NF- $\kappa$ B: Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1; EGFR: Epidermal growth factor receptor.

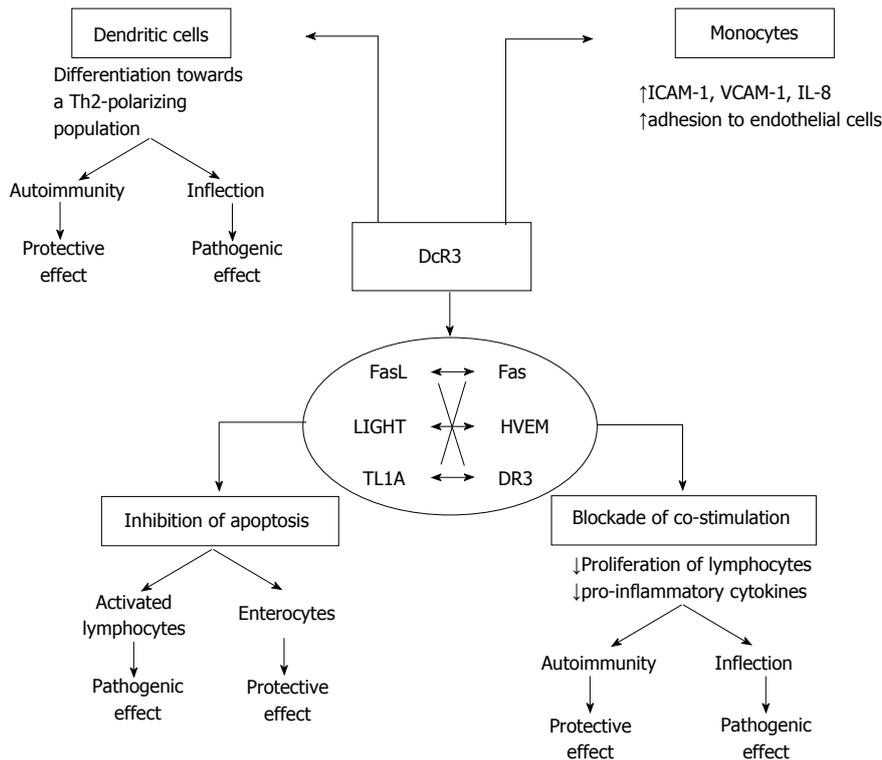
As these interactions usually lead to pro-inflammatory responses, an anti-inflammatory role has been attributed to DcR3. For example, DcR3 can ameliorate T-cell responses to alloantigens by neutralizing LIGHT-HVEM association<sup>[18]</sup>. Similarly, DcR3 is capable of attenuating T-cell activation and downregulating the secretion of proinflammatory cytokines mediated by TL1A/DR3 signaling<sup>[12]</sup>. There is recent evidence that DcR3 also has non-decoy, direct immunomodulatory properties. DcR3 induces polarization of antigen-presenting cells towards a Th2 immunophenotype with concomitant downregulation of their activation status, as indicated by reduced expression of HLA-DR and CD80/B7.1<sup>[19]</sup>. Along the same line, DcR3 was shown to divert macrophages towards an M2/immunosuppressive phenotype<sup>[20]</sup>. Furthermore, DcR3 facilitates adhesion of circulating monocytes to the endothelium by upregulating the expression of intercellular adhesion molecule-1, vascular cell adhesion molecule 1 and interleukin (IL)-8 through NF- $\kappa$ B-mediated mechanisms<sup>[21]</sup>. This may lead to enhanced homing of cells to inflammatory foci.

Collectively, these data indicate that DcR3 exerts pleiotropic roles during inflammatory disorders (Figure 2). DcR3 is usually undetectable in the sera of healthy in-

dividuals but becomes detectable and/or highly elevated during a number of diseases characterized by chronic inflammation. Although the association between elevated serum DcR3 concentration and chronic inflammatory disorders is indisputable, several critical questions remain unanswered. First, it is often unclear whether the elevated DcR3 protein exerts protective or pathogenic roles during specific immunological conditions, given the vast array of functions that have been attributed to this molecule. Second, the pathogenetic relevance of such systemic elevations of DcR3 may not be easily recognized, as this may be a secondary phenomenon related to the presence of inflammation and not a causative factor. Moreover, the specific disease state may be of critical importance, with DcR3 exerting pro- or anti-inflammatory effects in different settings. In the remaining of this article the strongest associations of DcR3 with inflammatory disorders will be reviewed (Table 1).

### Rheumatologic diseases

Increased secretion of DcR3 has been reported in several rheumatologic conditions. A strong association has been described for SLE. Indeed, serum DcR3 is significantly



**Figure 2 Dual immunomodulatory function of Decoy receptor 3.** Decoy receptor 3 (DcR3) displays several properties that are of pathogenetic relevance during inflammatory reactions. The final effect may be either protective or pathogenic depending on several parameters, such as the specific condition (autoimmunity vs infection) and the cell type (lymphocyte, monocyte, epithelial cell). The majority of these effects are associated to the function of DcR3 as a decoy receptor, which inhibits signalling via the tumor necrosis factor superfamily ligands FasL, lymphotoxin-like inducible protein that competes with glycoprotein D for herpesvirus entry on T cells (LIGHT), and tumor necrosis factor-like molecule 1A (TL1A), through competition for ligand binding with the respective functional receptors Fas, herpesvirus entry mediator (HVEM), and DR3. DcR3 inhibits apoptosis induced by ligand/receptor interactions, which may have either deleterious or beneficial effects depending upon the specific cellular component. In particular, blockade of apoptosis in activated effector lymphocytes would lead to perpetuation of chronic inflammatory injury. On the other hand, it may induce the survival of intestinal epithelial cells in inflammatory bowel disease, leading to tissue protection. DcR3 may also interfere with effector immunological responses in several ways. It blocks LIGHT/HVEM- or TL1A/DR3-mediated co-stimulation of activated lymphocytes, leading to impaired proliferation and defective cytokine production. Such an effect may have direct anti-inflammatory function during autoimmune diseases. On the opposite, in the event of an infection such defects in effector lymphocyte activation may lead to impaired clearance of the microorganism and enhanced severity of the infection. The same duality takes place in relation to the effect of DcR3 on dendritic cell differentiation towards a Th2-polarizing antigen-presenting-cell subtype, which is a non-decoy function, as it occurs independently of binding to FasL, LIGHT or TL1A. Such Th2 polarization may dampen Th1-type pro-inflammatory responses in autoimmunity, but may lead to defective anti-microbial function during infections. An inverse correlation may occur for the effects of DcR3 on monocytes that include upregulation of the adhesion molecules intercellular adhesion molecule-1 and vascular cell adhesion protein-1 and enhanced adherence to endothelial cells. This may offer an advantage during infection via the recruitment of inflammatory cells; at the same time, however, it may be deleterious during autoimmune inflammation as it may lead to the constant homing of monocytes to the inflammatory foci and perpetuation of tissue injury. ICAM-1: Intercellular adhesion molecule-1; VCAM-1: Vascular cell adhesion protein-1.

elevated in patients with SLE as compared with healthy controls<sup>[22,23]</sup>. In one study, serum DcR3 levels were elevated in 43% of 90 SLE patients and only 2.4% of 123 healthy individuals<sup>[23]</sup>. More importantly, patients with active disease (SLE disease activity index  $\geq 10$ ) had higher concentrations than patients in remission (SLE disease activity index  $< 10$ ), indicating a positive correlation between sDcR3 concentration and disease activity<sup>[22]</sup>. This is further supported by the fact that, when compared with DcR3-negative SLE patients, a larger percentage of DcR3-positive patients showed abnormally high serum IgE levels, which serves as a surrogate marker of ongoing Th2 immune responses<sup>[23]</sup>. The potential involvement of DcR3 in the pathogenesis of SLE is supported by studies in mice expressing a human DcR3 transgene under the control of an actin promoter<sup>[24]</sup>. These mice develop a SLE-like syndrome sharing characteristic features of the human condition, including autoantibodies against

double-stranded DNA, glomerular nephritis with IgG and C3 deposition, skin lesions, SLE-like hepatopathy and pancytopenia. This clinical similarity was associated with parallel immunological disturbances as well. Indeed, DcR3 transgenic mice demonstrated dominant Th2 associated features such as enhanced IL-4 expression and elevated serum IgE levels. Of particular interest is the fact that penetrance of this murine syndrome was, like SLE, sex-associated, as it was described in 60% of females vs in only 20% of males<sup>[24]</sup>. Subsequent studies from the same group showed that the murine clinical and immunological SLE-like syndrome was transmissible to irradiated C57BL/6 female mice upon transplantation of T-cell-depleted bone marrow from DcR3 Tg mice<sup>[25]</sup>. These findings showed that DcR3 secreted from cells of hematopoietic origin induces a SLE-like syndrome in mice. Although the exact pathogenetic role of DcR3 in SLE remains to be determined, at least two mechanisms have

**Table 1** Expression profile of decoy receptor 3 in chronic inflammatory diseases and potential as a biomarker

Disease	Expression of DcR3	Utility as biomarker
Systemic lupus erythematosus <sup>[22,23]</sup>	Serum	Higher levels in active disease than in remission
Rheumatoid arthritis <sup>[26-29,32]</sup>	Serum Synovial fluid Fibroblast-like synoviocytes Inflamed synovium	Correlates with disease stage "Undetectable DcR3/low TL1A" serotype may predict lack of atheromatic plaque formation/progression in RA patients
Systemic sclerosis <sup>[34]</sup>	Serum	Higher levels in diffuse cutaneous systemic sclerosis than in limited cutaneous disease Correlates with markers of right ventricular function Correlates with inflammatory markers (CRP, ESR)
Osteoarthritis <sup>[27,28,35]</sup>	Serum Chondrocytes	
Ulcerative colitis <sup>[37,38]</sup>	Inflamed colon Lamina propria T cells	Higher levels in active disease than in remission Decrease in serum levels in response to treatment
Crohn's disease <sup>[7,39]</sup>	Serum Inflamed colon Inflamed ileum Small Intestinal epithelium Mononuclear and endothelial cells next to mucosal ulcers	Higher levels in active disease than in remission Decrease in serum levels in response to treatment
Appendicitis <sup>[8]</sup>	Serum Epithelium of inflamed appendix	
Sepsis <sup>[9,43]</sup>	Serum Monocytes	DcR3 levels may discriminate sepsis <i>vs</i> SIRS Correlates with APACHE II score
Tuberculosis <sup>[42]</sup>	Myeloid-derived dendritic cells Serum	High serum levels predictive of development of active disease in patients with latent tuberculosis High serum levels associated with poor prognosis High serum levels predictive of multiple organ failure and 28-d mortality
ARDS <sup>[44]</sup>	Serum	
Atopic dermatitis <sup>[48]</sup>	Serum	
Psoriasis <sup>[49,50]</sup>	Psoriatic lesions Keratinocytes Macrophages Perivascular areas	
Liver disease <sup>[45]</sup>	Regenerative and dysplastic nodules in cirrhosis	
Multiple sclerosis <sup>[51]</sup>	Cerebrospinal fluid	
Chronic peritoneal dialysis <sup>[46]</sup>	Serum	High serum levels predictive of peritonitis
Silicosis <sup>[53]</sup>	Peripheral blood mononuclear cells	

DcR3: Decoy receptor 3; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; SIRS: Systemic inflammatory response syndrome; APACHE: Acute physiology and chronic health evaluation; ARDS: Acute respiratory distress syndrome.

been proposed. Firstly, DcR3 may inhibit FasL-mediated apoptosis in activated T cells. In turn, this may result in impaired activation-induced cell death of T cells, leading to their enhanced survival and intensification of effector pathways. Along that line, missense mutations have been recently identified in adult and juvenile patients with SLE, which resulted in altered binding kinetics to FasL and significantly increased lymphocyte proliferation<sup>[25]</sup>. Furthermore, in the previous study with DcR3 transgenic mice it was shown that recombinant DcR3 or endogenous DcR3 produced by transgenic T cells protected T cells from activation-induced apoptosis *in vitro*<sup>[24]</sup>. Secondly, co-stimulation of T cells with soluble DcR3-Fc increased IL-2 and interferon-gamma production. Furthermore, T Lymphocytes isolated from patients with SLE displayed enhanced reactivity to DcR3. Thus, DcR3 seems to be responsible at least partly for T cell hyper-reactivity in SLE both by preventing apoptosis induced by cell-activation as well as by providing co-stimulatory signals<sup>[22]</sup>.

DcR3 expression is also elevated in RA. Previous studies have shown that DcR3 protein is more frequently detected in the sera of patients with RA than in healthy controls<sup>[26]</sup>. In addition, the mean DcR3 concentration is significantly higher in RA (*vs* healthy controls) and, more significantly, it correlates with severe RA stage<sup>[26]</sup>. In another study sDcR3 was found to be significantly higher in patients with RA than in those with osteoarthritis<sup>[27]</sup>. Furthermore, DcR3 is also detected in the synovial fluid of patients with inflammatory arthritis, including RA, ankylosing spondylitis and osteoarthritis<sup>[26-28]</sup>. In addition, DcR3 mRNA transcripts were detected in fibroblast-like synoviocytes isolated from patients with RA or osteoarthritis<sup>[29]</sup>. A recent study further characterized the distribution of DcR3 expression in the inflamed synovium<sup>[28]</sup>. It was shown that no significant differences were observed in synovial lining layer between RA, ankylosing spondylitis and osteoarthritis. On the other hand, at the sublining layer, the expression of DcR3 was more upregulated

in RA and AS than in osteoarthritis. Taken together, the increased local production of DcR3 at the inflamed synovium raises the possibility that this protein participates in the pathogenesis of arthritis. This hypothesis is, in fact, supported by recent experimental evidence. Firstly, DcR3 was shown to inhibit FasL-mediated apoptosis of fibroblast-like synoviocytes<sup>[29]</sup>. Secondly, expression of DcR3 was highly upregulated by TNF- $\alpha$ , a cytokine with a pivotal role in the pathogenesis of RA. Indeed, in one study, serum DcR3 concentrations strongly correlated with the respective TNF- $\alpha$  values<sup>[27]</sup>; furthermore, TNF- $\alpha$  induced the expression of DcR3 in synoviocytes, an effect that was specific for RA, as it was not observed in osteoarthritis<sup>[29]</sup>. Thirdly, a protective role for DcR3 in experimental collagen-induced arthritis was recently proposed<sup>[30]</sup>. Forced over-expression of DcR3 in mice *via* plasmid transfer resulted in significantly attenuated arthritis severity, combined with downregulated immunological responses. The latter included a smaller size of inguinal lymph nodes, lower numbers of CD19<sup>+</sup> B cells and interferon (IFN)- $\gamma$ , IL-4, IL-17A, and Foxp3-positive CD4<sup>+</sup> T cells and decreased circulating IL-6. Finally, a protective role for DcR3 was also implicated by a recent *in vitro* study, which reported that DcR3 was capable of binding to TL1A expressed on fibroblast-like synoviocytes from RA patients and inhibited their proliferation induced by pro-inflammatory cytokines<sup>[31]</sup>. In all, the aforementioned experimental and clinical evidence indicates that DcR3 may be of pathogenetic relevance in RA. A further intriguing possibility arose from a study from our group that examined the predictive value of DcR3 (and its ligand TL1A) for atheromatic plaque formation in patients with RA<sup>[32]</sup>. In this study, 45 patients had a baseline measurement of TL1A and DcR3 serum concentration and were prospectively followed up for more than 3 years with ultrasound of carotid and femoral arteries. It was shown that a serum phenotype of “low TL1A and undetectable DcR3” was predictive of significantly fewer newly formed carotid plaques during the next 3.5 years and a preserved atherosclerosis profile in carotid or carotid and/or femoral arteries. This study expands previous work on the role of the TL1A/DR3/DcR3 pathway in atherogenesis<sup>[33]</sup>, and indicates that serial measurements of these proteins in the serum may serve as biomarkers of low-grade systemic inflammation and predict the future risk for plaque formation in RA patients.

Recently, an association was also described between serum DcR3 and systemic sclerosis (SSc)<sup>[34]</sup>. It was found that patients with diffuse cutaneous SSc had significantly higher serum DcR3 concentrations than healthy controls or those with limited cutaneous disease. The authors concluded that, in SSc, soluble DcR3 values may serve as a surrogate biomarker of pulmonary arterial hypertension and systemic inflammation due to its significant correlation with indicators of right ventricular function or of systemic inflammation (CRP, ESR, and IgG), respectively.

Apart from its involvement in the pathogenesis of arthritis, DcR3 may also interfere with bone metabolism,

as suggested by recent studies. DcR3 is expressed in chondrocytes and affects their proliferation *via* Extracellular Signal-Regulated Kinase signaling and Fas-induced apoptosis<sup>[35]</sup>. Thus, DcR3-mediated pathways may interfere with cartilage regeneration, whereas DcR3 manipulation may offer therapeutic opportunities for people with osteoarthritis. In addition, DcR3 has also been shown to promote formation of osteoclasts from monocytes, macrophages, and bone stromal marrow cells<sup>[36]</sup>. Mechanistic evidence for such a function was shown in DcR3 transgenic mice which displayed significantly lower bone mineral density and total body bone mineral content when compared with controls. Furthermore, local administration of DcR3 resulted in decreased bone volume. These data indicate an effector role for DcR3 in inducing osteoclast formation and bone resorption activity, and suggest that manipulation of DcR3 expression/signaling may be a therapeutic option for restoring bone metabolism and prevent/reverse osteoporosis<sup>[36]</sup>.

### IBD

The association of DcR3 with chronic inflammatory diseases of the gastrointestinal tract, in particular ulcerative colitis (UC) and Crohn's disease (CD) has been extensively studied. A first study in UC reported increased immunostaining for DcR3 protein (and for other decoy receptors) at inflamed intestinal regions, but not at healthy colon<sup>[37]</sup>. T-cells were the major source of DcR3 expression. Similar upregulation of DcR3 was demonstrated in CD<sup>[7]</sup>. In particular, DcR3 mRNA transcripts were increased in the small intestinal epithelial compartment of areas affected by CD as compared to non-inflamed controls. Furthermore, Western-blot analysis detected elevated expression of DcR3 protein in areas with active CD. Immunohistochemical analysis revealed increased localization of DcR3 to follicle-associated epithelial cells in areas with CD-related inflammation. Additional staining was observed in mononuclear and endothelial cells in the vicinity of ulcerative lesions<sup>[7]</sup>. It should be noted that elevated expression of DcR3 was also reported in the epithelium of acutely inflamed appendices, suggesting a stimulatory effect of mucosal inflammation to the local expression of DcR3<sup>[8]</sup>. Recent studies from our group have confirmed the elevated mucosal expression of DcR3 mRNA in areas with CD-or UC-related inflammation in comparison to either healthy controls or non-inflamed areas from IBD<sup>[38,39]</sup>.

The aforementioned studies provided information regarding the functional importance of DcR3 in IBD. The central pathophysiological hypothesis is that mucosal DcR3 interferes with FasL-mediated apoptosis of lamina propria T cells. This would be pathogenic as it would lead to increased survival of effector lymphocytes and perpetuation of pro-inflammatory responses. Interestingly, the mucosal expression of DcR3 significantly correlated with that of TL1A and Fas-L, indicating that DcR3 is upregulated in response to an initial increase of its ligands and, by blocking functional signaling through DR3 and Fas,

exerts anti-apoptotic function<sup>[39]</sup>. At the same time, however, DcR3 also protected small-intestinal epithelial cells from apoptosis, an effect that would lead to beneficial effects. Taken together these studies may imply that DcR3 exerts dichotomous functions at the intestinal mucosa depending on the particular conditions and the specific cellular localization.

The potential of DcR3 as a biomarker for disease activity in IBD was also tested. The concentration of DcR3 in the serum was found significantly elevated in patients with active IBD (UC or CD)<sup>[7,38,39]</sup>. This was evident in comparison with either IBD-patients in remission or healthy individuals. More importantly, when pre- and post-treatment values in the same patient were measured, we found that effective anti-inflammatory treatment resulted in almost complete disappearance of sDcR3 from the systemic circulation. This decrease paralleled a similar reduction in CRP concentration<sup>[38]</sup>. Interestingly, in the study by Funke *et al*<sup>[7]</sup>, TNF- $\alpha$  was shown to be a potent inducer of DcR3 expression. Accordingly, blockade of TNF- $\alpha$  with neutralizing monoclonal antibodies resulted in significant downregulation of the systemic expression of DcR3 in both RA and UC<sup>[26,38,39]</sup>. The systemic expression of DcR3 may also be affected by the presence of IBD-associated polymorphisms in the *tnfrsf6b* gene. In recent studies such polymorphisms were associated with early-onset IBD. Interestingly, these polymorphisms resulted not only with higher mucosal expression of DcR3 mRNA but also in elevated circulating levels of this protein<sup>[40]</sup>.

Taken together, these studies indicate that DcR3 is expressed at the intestinal mucosa, becomes highly upregulated in active inflammatory lesions and is shed to the systemic circulation during active IBD. Larger studies will be needed to further clarify its potential for use as a sensitive biomarker of active disease and whether serial measurements may have a predictive value for response to treatment.

## INFECTIOUS DISEASES

The role of DcR3 in infection has been studied in depth and its potential as a biomarker during septic conditions has been intensively sought. One of the first studies reported significantly elevated serum concentrations of patients with various infectious diseases when compared with healthy controls<sup>[9]</sup>. Further supporting an association between infectious disease and DcR3, it was shown that the major DcR3 producers were monocytes and myeloid-derived dendritic cells which released DcR3 upon stimulation with bacterial products from both gram-positive and gram-negative microorganisms *via* Toll-like receptor -2 and -4 signaling<sup>[9]</sup>. This elevated DcR3 expression following infection may have negative results for the outcome of bacterial disease as it was shown by studies in DcR3 transgenic mice, which demonstrated a defect in developing a Th1-type response<sup>[41]</sup>. In particular, splenocytes from transgenic mice displayed upregulation of IL-4 and IL-10 and down-regulation of IFN- $\gamma$ , IL-12,

and TNF- $\alpha$  upon stimulation *in vitro* by influenza hemagglutinin peptide. More importantly, these mice showed increased susceptibility to infection with *Listeria monocytogenes*, accompanied with reduced expression of IFN- $\gamma$ . Therefore, a Th2-type bias of immune responses in the face of elevated expression of DcR3 may lead to defective clearance of microorganisms that are eliminated *via* Th1-based cell-mediated immunity. Findings from a recent study in tuberculosis support this hypothesis<sup>[42]</sup>. In this work it was shown that high DcR3 serum levels in conjunction with high prostaglandin-2 and low lipoxin levels, predicted with adequate sensitivity the development of active tuberculosis in patients with the latent form of the disease. Interestingly, high serum DcR3 expression correlated with a poorer prognosis. Thus, DcR3 may serve as an indicator of inadequate confinement of latent tuberculosis either through suppression of Th1 responses or through regulation of apoptotic pathways<sup>[42]</sup>.

Two recent studies looked at the validity of DcR3 serum concentration as a prognostic marker for disease outcome in septic conditions. In the first study, DcR3 levels were found to accurately distinguish sepsis from systemic inflammatory response syndrome (SIRS)<sup>[43]</sup>. Receiver-operating characteristic curves analysis was conducted and a cut-off value of DcR3 concentration was proposed which predicted sepsis from SIRS with 96% sensitivity and 82.6% specificity. DcR3 concentration in the peripheral blood was also correlated positively with the APACHE II score; one of the most commonly used indexes for the quantification of sepsis severity. These results were complementary to findings from another study that reported DcR3 as a valuable predictor of adverse outcome in patients with acute respiratory distress syndrome (ARDS)<sup>[44]</sup>. Indeed, from a variety of biomarkers tested, only DcR3 serum concentration discriminated those patients with multiple organ failure and mortality within 28-d from survivors. The predictive value of DcR3 was evident from the first week of ARDS. The interpretation of these results may be two-fold and indicate that elevation of DcR3 may be an epiphenomenon resulting from increased secretion of this protein by inflammatory cell-populations. Alternative DcR3 may also be pathogenetically implicated *via* its known immunomodulatory effects which include apoptosis of dendritic cells, suppression of HLA-DR surface expression and diversion of the Th1/Th2 balance towards Th2 responses.

## OTHER DISEASES

Although not as well-studied as the conditions mentioned in the previous sections, DcR3 tissue and systemic expression has been reported for several other non-neoplastic conditions. In chronic liver disease, DcR3 was expressed mainly in biliary epithelial cells and infiltrating lymphocytes<sup>[45]</sup>. The main DcR3 localization was observed in regenerative and dysplastic nodules of cirrhotic livers. The elevated expression of DcR3 in chronic liver disease, insinuates a role for this molecule in the chronic hepatitis-cirrhosis-hepatocellular carcinoma sequence,

possibly *via* the modulation of apoptosis of hepatocytes<sup>[45]</sup>. In the renal system dual roles has been attributed to DcR3 according to the specific clinical scenario. A prospective cohort study in patients receiving chronic peritoneal dialysis demonstrated that elevated circulating DcR3 levels are associated with increased risk for subsequent peritonitis, and may serve as an independent predictor for this, often fatal, complication<sup>[46]</sup>. On the other hand, DcR3 expression may have beneficiary effects in IgA nephropathy. In an animal model of this disease DcR3 plasmid administration and subsequent DcR3 protein expression, prevented the clinical onset of nephropathy<sup>[47]</sup>. DcR3 was found to act on multiple steps of the disease process, mainly *via* the systemic modulation of T cell activation/proliferation but also *via* the prevention of mononuclear leukocyte infiltration and apoptosis in the kidney. In dermatology, it was reported that serum DcR3 is elevated in patients with atopic dermatitis<sup>[48]</sup>. In addition, DcR3 was over-expressed in skin lesions from patients with psoriasis<sup>[49]</sup>. Cells staining positive for DcR3 protein expression were among those that are critically involved in the pathogenesis of chronic skin inflammation, such as keratinocytes, macrophages in deep dermis and cells at the perivascular area<sup>[49]</sup>. Recently it was reported that up-regulation of DcR3 in keratinocytes is driven by epidermal growth factor receptor, further supporting a potential pathogenetic importance in psoriasis<sup>[50]</sup>. DcR3 was also elevated in cerebrospinal fluid samples from patients with multiple sclerosis and other inflammatory neurological diseases in comparison with patients with herniated discs<sup>[51]</sup>. This finding prompted an investigation of the therapeutic potential of DcR3 in mice with experimental autoimmune encephalomyelitis by administering DcR3 intrathecally<sup>[52]</sup>. This intervention improved significantly the neurological symptoms and ameliorated inflammation in the spinal cord. These findings were replicated in an adoptive transfer study that showed that splenocytes from DcR3-treated mice retained the ability to influence positively the course of the disease. These effects were attributed to the modification of effector T-cell responses, with a shift towards elevated numbers of Th2 and decreased Th1 and Th17 cells<sup>[52]</sup>. Finally, DcR3 was studied also in silicosis. It was reported that the DcR3 gene mRNA was significantly overexpressed in the peripheral blood mononuclear cells of patients with silicosis in comparison to healthy controls<sup>[53,54]</sup>. The authors suggested that a fraction of CD4<sup>+</sup> T lymphocytes expresses low levels of membrane Fas and secretes significantly higher levels of DcR3 along with soluble Fas and spliced shorter variants, resulting in considerable resistance to anti-Fas autoantibody-induced apoptosis.

## CONCLUSION

The importance of DcR3 as an immunological biomarker has been emphasized in recent years. Indeed, its application appears to be advantageous due to several reasons. First, DcR3 exists only as a secreted protein, therefore, fluctuations of its expression are easily detected and

measurable in the peripheral blood. Second, in healthy conditions, its expression is minimal in most tissues as it is usually absent or very low at the systemic circulation. Detecting, therefore, elevated amounts of DcR3 protein in the serum is usually indicative of an ongoing inflammatory response, when neoplasms have been excluded. Third, soluble DcR3 concentration appears to respond better to the presence of inflammation than the levels of the corresponding ligands. Fourth, DcR3 levels in the systemic circulation are usually associated with disease severity. As mentioned above, patients with active/severe forms of SLE, RA, IBD, SSc, infections and ARDS have significantly higher levels of serum DcR3 than patients with milder forms of the disease. Therefore, elevated DcR3 levels may serve as an adverse prognostic factor. Finally, anti-inflammatory treatment, including biological therapies leads to a definitive decrease in soluble DcR3. This indicates that DcR3 may be useful as marker of response to treatment. In all, DcR3 holds great promise to become a useful biomarker for the estimation of disease activity and follow-up of treatment responses in patients with various inflammatory diseases.

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