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INVITED REVIEW ARTICLE

# Dendritic cell immunoreceptors: C-type lectin receptors for pattern-recognition and signaling on antigen-presenting cells

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**Summary** C-type lectin receptors are equipped on phagocytes for antigen capturing. Some of them seem to have a major role in cellular activation, rather than antigen internalization. The dendritic cell (DC) immunoreceptor (DCIR) and DC-associated C-type lectin (dectin)-1 have been identified as prototypic DC-associated C-type lectin receptors, characterized by their signaling mechanisms through distinct intracellular motifs; the former contains the immunoreceptor tyrosine-based inhibitory motif (ITIM), to act as an inhibitory receptor, whereas the latter works as an activating receptor via its immunoreceptor tyrosine-based activation motif (ITAM). Genes of both receptors are localized very close to the natural killer (NK) gene complex (NKC), in which genes of lectin-type activating and inhibitory NK cell receptors are clustered. Recently, the gene of the DC immunoactivating receptor (DCAR) has been identified next to the DCIR gene, and this acts as a putative activating pair of DCIR through association with an ITAM-bearing Fc receptor (FcR) $\gamma$ chain. On the other hand, the gene of an ITIM-bearing myeloid inhibitory C-type lectin-like receptor (MICL) has been found close to the dectin-1 gene. The genes of other homologous DC-associated C-type lectin receptors, dectin-2 and blood DC antigen (BDCA)-2, form a cluster with those of DCIR and DCAR, while the dectin-1 gene cluster contains lectin-like oxidized low-density lipoprotein receptor (LOX)-1, C-type lectin-like receptor (CLEC)-1 and 2, as well as MICL. Although no ligand of DCIR has yet been identified, dectin-1 recognizes fungal $\beta$-glucan and its critical role in the biological effects of $\beta$-glucan has been vigorously investigated. In this review, the characteristic features of these DCIR and dectin-1 family lectins, including the signaling mechanisms, ligand recognition and

*Abbreviations:* APC, antigen-presenting cell; BCR, B cell receptor; CHS, contact hypersensitivity; CLEC, C-type lectin domain family; CRD, carbohydrate recognition domain; CTLD, C-type lectin-like domain; DC, dendritic cell; FcR, Fc receptor; IFN, interferon; Ig, immunoglobulin; IL, interleukin; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; LC, Langerhans cell; LPS, lipopolysaccharide; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; moDC, monocyte-derived DC; NF, nuclear factor; NK, natural killer; NKC, NK gene complex; OxLDL, oxidized low-density lipoprotein; PDC, plasmacytoid DC; PRR, pattern-recognition receptor; PTK, protein tyrosine kinase; SH2, Src homology 2; SHP, SH2 domain-containing protein tyrosine phosphatase; TCR, T cell receptor; TLR, Toll-like receptor; UV, ultraviolet

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regulation of cellular functions, are summarized and the term "DC immunoreceptors" is applied to a distinct set of signaling pattern-recognition receptors described here.


**Contents**



## 1. Pattern-recognizing C-type lectin receptors on macrophages and DCs

In the innate immune system, pattern-recognition receptors (PRRs), germline-encoding receptors recognizing pathogen-associated molecular patterns (PAMPs), have critical roles in protection from invading pathogens. Toll-like receptors (TLRs), a large family of molecules which are the mammalian homologues of drosophila Toll, were identified as the major PRRs with strong activating capacity and have been intensively investigated for the last decade [1]. Recently, an increasing number of nonTLR PRRs, together with their pathophysiological roles, have been identified [2]. In particular, cytosolic nucleotide-binding oligomerization domain (NOD) proteins, which are homologous to the plant disease-resistance (R) proteins and which bear similar C-terminal leucine-rich repeats (LRR) to TLRs, have been shown to form a large family and to be relevant to the pathogenesis of certain inflammatory diseases [3].

Dectin (DC-associated C-type lectin)-1 is another example that recognizes fungal β-glucan and has a collaborative effect with TLR2 on yeast-induced activation signals [4]. In general, C-type lectins are classical molecules that are defined by their ability to bind carbohydrates in a $Ca^{2+}$-dependent manner [5]. Soluble and membrane-bound proteins are included in this family and the family members share a common domain structure, named the carbohydrate recognition domain (CRD), which contains 18 highly conserved amino acid residues including two-folds of disulfide bonds, formed by four cysteine residues. Phagocytes, such as macrophages and DCs, express many kinds of C-type lectin receptors on their cell surfaces for antigen capture [6]. Based on their molecular structures, they are divided into two large groups.

One group, called the mannose receptor (MR) family, is a type I transmembrane protein with multiple CRDs, including the MR (CD206), DEC-205 (CD205), phospholipase A2 receptor and Endo 180 (CD280) [7]. They commonly consist of an N-terminal cysteine-rich domain and a fibronectin type II domain as well as 8 or 10 CRDs. Since not all of their multiple CRDs have been shown to bind $Ca^{2+}$ or carbohydrates, the term C-type lectin-like domain (CTLD) is used to describe the domain without $Ca^{2+}$-dependent sugar-binding capacity. The amino acid sequence of CTLD is closely related to that of CRD, but conservation of the common 18 amino acid residues is incomplete.

The other group, called the asialoglycoprotein receptor (ASGPR) family, comprises type II transmembrane proteins with a single CRD, such as macrophage galactose-type C-type lectin (MGL,