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Review

C-type lectin DC-SIGN: An adhesion, signalling and antigen-uptake molecule that guides dendritic cells in immunity

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ABSTRACT

The dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) is a type II C-type lectin whose expression is restricted to the most potent antigen-presenting cells (APCs), the dendritic cells (DCs). In recent years, DC-SIGN has gained an exponential increase in attention because of its involvement in multiple aspects of immune function. Besides being an adhesion molecule, particularly in binding ICAM-2 and ICAM-3, it is also crucial in recognizing several endogenous and exogenous antigens. Additionally, the intracellular domain of DC-SIGN includes molecular motifs, which enable the activation of signal transduction pathways involving Raf-1 and subsequent modulation of DC-maturation status, through direct modification of nuclear factor Nf-κB in DCs. Upon DC-SIGN engagement by mannose- or fucose-containing oligosaccharides, the latter leads to a tailored Toll-like receptor signalling, resulting in an altered DC-cytokine profile and skewing of Th1/Th2 responses. In this article, we will discuss recent advances on a broad perspective concerning DC-SIGN structure, signalling and immune function.

Contents

Abbreviations: (APCs), antigen-presenting cells; (CRD), carbohydrate recognition domain; C(CLRs), C-type lectin receptors; (CBP), CREB-binding protein; (CRD), cysteine-rich domain; (DC-SIGN), dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; (HATs), histone acetyltransferases; (HDACs), histone deacetylases; (ICAM), intracellular adhesion molecule; (Le^x), Lewis-x; (ManLAM), mannosylated lipoarabinomannan; (LPS), lipopolysaccharide; (SEA), soluble egg antigen; (TLR), Toll-like receptor; (Pak), p21-activated kinases; (PRR), pathogen recognition receptor.

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1. Introduction

Dendritic cells (DCs) are a heterogeneous population and the most potent antigen-presenting cells (APCs) known so far [1]. The functional characteristics of DCs are unique in that they are responsible for generating strong Ag-specific immune responses, as well as for inducing tolerance and maintenance of immune homeostasis. Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) is a type II transmembrane lectin receptor. Attention on DC-SIGN has increased greatly in recent years due to important discoveries documenting its immune-related functions and cell-specific expression that is mostly restricted to DCs. DC-SIGN is abundantly expressed on immature DCs (iDCs) that are present in peripheral tissues, but is also found, albeit down-regulated, on mature or activated DCs (mDCs) in lymphoid tissues such as lymph nodes, tonsils and spleen [2]. However, it is not expressed on certain DC-types such as follicular DCs or on skin-resident Langerhans DCs.

Although C-type lectin receptors (CLRs) were initially thought to function as scavenger receptors that bind various pathogens upon recognition of particular carbohydrate profiles, it has become clear that some C-type lectins may function as adhesion, signalling or antigen receptors. CLRs are well known for their function of serving as antigen-uptake receptors, and this is consistent with the fact that most CLRs are present on APCs [3]. In addition, several CLRs have been shown to contribute to loading of endocytosed Ags on MHC class I and class II molecules, thereby facilitating effective Ag-specific CD4 and CD8 T-cell responses [4,5]. Besides foreign Ags, DC-SIGN binds to a number of endogenous ligands, particularly to intracellular adhesion molecules (ICAM)-2 on endothelial cells and ICAM-3 on T lymphocytes, contributing to transendothelial migration of DCs and the formation of the DC–T cell synapse, respectively [2,6]. Apart from supporting the initial immune response between DCs and T cells, DC-SIGN also recognizes several bacterial pathogens [7], contributing to generation of pathogen-tailored immune responses. Furthermore, DC-SIGN can capture HIV-1 at entry sites and transport the virus into lymphoid tissues, where HIV-1 can be transmitted to $CD4^+$ T cells. Recently, it has been demonstrated that, besides adhesive and Ag-recognition properties, engagement of DC-SIGN on DCs results in activation of signal transduction pathways that can cause extensive modulation of immune responses, particularly when co-activated with Toll-like receptor (TLR)-induced signalling [8]. Whereas simultaneous signalling through TLRs is present during pathogen-specific immune responses during infection [9], both in vitro and in vivo targeting to CLRs on immature DCs leads to tolerance by default. The physiological function of DC-SIGN may thus be induction of tolerance by immature DC, after recognition of glycosylated self-antigens, for homeostatic control [10]. Several pathogens that target DC-SIGN appear to exploit this signalling and subvert its functions, either by inhibition of antigen presentation or by alteration of TLR mediated signalling, resulting in modification of T cell responses [11]. In this review, we will discuss the structural, functional and signalling characteristics of DC-SIGN in the context of its functions in immune regulation, tumour immunity and potential therapy.

2. DC-SIGN structure and expression on the DC surface

2.1. DC-SIGN expression

DC-SIGN is preferentially expressed on myeloid DCs and is found on dermal DCs, interstitial DCs, a subset of blood DCs, and on *in vitro* prepared, monocyte-derived DCs [12,13]. Due to its highly restricted expression, DC-SIGN is considered a DC-specific phenotypic marker. During *in vitro* differentiation of DCs from monocytes, DC-SIGN expression is dependent on IL-4 signalling [14]. Furthermore, IL-4 and IL-13 (both of which act through the STAT6 signalling pathway) can also cause *de novo* expression of DC-SIGN on the THP-1 monocytic cell line, primary monocytes and, alternatively, activated macrophages [15]. Pre-treatment of THP-1 cells with differentiation-inducing agents such as phorbol esters and bryostatin further conveys the DC-SIGN-inducing ability of IL-4. In accordance with the study of Relloso et al. [15], our group recently demonstrated that the surface expression of DC-SIGN on monocytes appears as early as 24 h after GM-CSF and IL-4 induced DC differentiation, and reaches peak levels on day four (Svajger et al., unpublished observations). The JAK-STAT signalling route is involved in IL-4-dependent induction of DC-SIGN. The use of tryphostin AG490, a specific inhibitor of JAK2 and JAK3, results in complete abrogation of DC-SIGN induction [14]. Thus, it can be speculated that STAT6, as a major IL-4 signalling element, is directly responsible for binding to promoter regions of the DC-SIGN gene and induction of transcription. Furthermore, IFN-α and IFN-γ inhibit the up-regulation of DC-SIGN by IL-4, and both cytokines have been demonstrated to suppress IL-4-dependent gene expression by inhibiting tyrosine phosphorylation and nuclear translocation of STAT6, most probably via induced expression of suppressors of cytokine signalling [16,17]. Considering the negative regulation of DC-SIGN expression by myeloid DCs, DC-SIGN was shown to be negatively regulated by type I and II interferons, as well as by the anti-inflammatory drug dexamethasone and TGF-β [14]. Dexamethasone blocks *in vitro* DC differentiation at the monocyte stage, resulting in $CD14^+$ macrophage-like cells [18]. It has been demonstrated that dexamethasone can interfere with the JAK-STAT pathway [19] indicating that prevention of DC-SIGN expression could be achieved by direct inhibition of IL-4 signalling. However, although TGF-β can inhibit the Jak-STAT activation in certain systems, it has been demonstrated that it fails to suppress STAT6 activation by IL-4 in monocytes [16]. This tells us that factors other than STAT6 are probably also involved in the regulation of DC-SIGN expression. The group of Corbi recently demonstrated that the transcription factor PU.1 regulates basal and tissue-specific expression of DC-SIGN through occupancy of two DNA elements within the proximal regulatory region of the DC-SIGN gene [20]. The expression of DC-SIGN correlated with nuclear levels of PU.1 transcription factor during DC maturation as well as during classical and alternative macrophage activation [20]. This finding further supports the connection between proper DC differentiation and DC-SIGN expression, since high PU.1 activity directs the differentiation of bone marrow progenitors and blood monocytes towards DCs and suppresses macrophage development [21].

2.2. DC-SIGN structure

DC-SIGN contains a carbohydrate recognition domain (CRD), a neck region composed of 7 and a half repeats containing 23 amino-acid residue repeats, and a transmembrane region followed by a cytoplasmic tail containing recycling and internalization motifs [2,22]. DC-SIGN ligation can result in transmission of intracellular signalling and this has been associated with the presence of a di-leucine motif and a tyrosine residue in the cytoplasmic tail [23].

The formation of multimeric complexes or, alternatively, conformational changes of their receptor is a possible way of increasing