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Review

The role of sialoglycans in modulating dendritic cell function and tumour immunity

Zélia Silva [a,b,d], Cátia O. Soares [a,c], Mariana Barbosa [a,b,d], Angelina S. Palma [a,c], Filipa Marcelo [a,c], Paula A. Videira [a,b,d,*]

[a] Institute for Health and Bioeconomy (i4HB), NOVA School of Science and Technology, Universidade NOVA de Lisboa, Caparica 2829-516, Portugal
[b] UCIBIO – Applied Molecular Biosciences Unit, Department of Life Sciences, NOVA School of Science and Technology, Universidade NOVA de Lisboa, Caparica 2829-516, Portugal
[c] UCIBIO – Applied Molecular Biosciences Unit, Department of Chemistry, NOVA School of Science and Technology, Universidade NOVA de Lisboa, Caparica 2829-516, Portugal
[d] CDG & Allies – Professionals and Patient Associations International Network (CDG & Allies – PPAIN), Department of Life Sciences, NOVA School of Science and Technology, Universidade NOVA de Lisboa, Caparica 2829-516, Portugal

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ABSTRACT

Dendritic cells (DCs) are crucial for initiating immune responses against tumours by presenting antigens to T cells. Glycosylation, particularly sialylation, plays a significant role in regulating cell functions, by modulating protein folding and signalling. This review aimed to provide a comprehensive overview of how sialic acids influence key aspects of DC biology, including maturation, migration, antigen presentation, and T cell interactions. Sialic acids influence DC endocytosis, affecting their ability to uptake and present antigens, while guiding their migration to lymph nodes and inflamed tissues. Removing sialic acids enhances DC-mediated antigen presentation to T cells, potentially boosting immune responses. Additionally, sialylated glycans on DCs modulate immune checkpoints, which can impact tumour immunity. Hypersialylation of tumour mucins further promotes immune evasion by interacting with DCs. Understanding the interplay between sialylation and DC functions offers promising avenues for enhancing cancer immunotherapy.

1. Introduction

Dendritic cells (DCs) are critical players in our immune system's defense against infections and cancer. As sentinels, DCs detect antigens, thereby initiating and regulating immune responses [1]. Their primary role is to capture and process antigens to present them to T cells, effectively bridging the innate and adaptive immune systems.

In the context of the tumour microenvironment (TME), the interplay between DCs and cancer cells is complex, and knowledge in this field is rapidly evolving. One area of particular interest is the role of sialic acid-carrying glycans known to contribute to a tumour-supportive environment. Curiously, in the TME, sialoglycans are often overexpressed in both neoplastic and immune cells, including DCs, modulating anti-tumour immune responses [2]. The presence of sialic acid on DC surface receptors modulates critical functions, including maturation and the ability to induce cytotoxic T cell [3–5]. Moreover, DCs recognise sialoglycans aberrantly expressed in cancer through inhibitory immune receptors, such as sialic acid-binding immunoglobulin-type lectins (Siglecs), further shaping the TME [6].

This review aims to highlight the crucial role of sialylated glycans in modulating DC function and anti-tumour immunity, emphasising how these interactions influence T cell function and contribute to tumour immune evasion. We also discuss emerging therapeutic strategies that target these glycans to enhance cancer immunotherapy. We seek to underscore the importance of understanding the role of sialoglycans in both DCs and cancer cells and their interactions in tumour immunology.

2. Dendritic cell function

2.1. The role of dendritic cells in the tumour microenvironment

Recent research highlights the TME as a critical factor in cancer

* Corresponding author at: Institute for Health and Bioeconomy (i4HB), NOVA School of Science and Technology, Universidade NOVA de Lisboa, Caparica 2829-516, Portugal.
E-mail address: p.videira@fct.unl.pt (P.A. Videira).

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progression and treatment. DCs play a crucial role in modulating tumour immunity due to their role in identifying antigens and priming T cells by presenting antigens through Major Histocompatibility Complex (MHC) molecules. The three main DCs subsets exhibit distinct functions in the TME. Myeloid/conventional DC type 1 (cDC1) are essential for cross-presenting tumour antigens to CD8+ T cells through MHC-I. cDC type 2 (cDC2) are characterised by high levels of MHC II and prime anti-tumor CD4+ T cells. Plasmacytoid DCs (pDC), depending on the context, can both promote or suppress antitumour immune responses [7–9].

Different DC subsets exhibit varying endocytic capabilities and antigen presentation efficiencies. After antigen endocytosis, and depending on the TME, DCs may initiate its maturation and expression of co-stimulatory molecules, such as CD86, and CD80 [10]. Each DC subset develops under specific transcription factors, and displays characteristic distinct surface markers [11], and cytokines that modify ongoing immune responses [12]. The interleukin (IL)-12 is required to develop T cell-mediated anti-tumour immunity [13]. Tumour-resident DCs, stimulated by type I interferon (IFN), produce chemokines, which are essential for recruiting T cells to the TME and for their activation and survival [14].

Due to their crucial role in immune cell responses to cancer, using DCs as anti-tumour immune therapy has shown promise in preclinical and clinical studies [15]. DCs loaded with specific tumour-associated antigens or whole tumour cells are the most common strategy of DC-based vaccines [16]. That is the case of sipuleucel-T, the FDA-approved cellular therapy using DCs activated *ex-vivo* to treat prostate cancer [17]. Yet, the specific conditions present in the TME may alter the action of DCs. TME devises many strategies that can have an impact on the recruitment and on the functions of DCs, such as the expression of immune checkpoint, small molecule mediators, metabolites, lack of secretion of pro-immunogenic and release of pro-tumorigenic cytokines and attraction of immuno-suppressive cells as revised in Mestrallet *et al.*, 2022 [8].

Therefore, understanding the complexity of TME and how it impacts the DCs functions and contributes to cancer immune evasion mechanisms offers promising potential for enhancing DC-based immunotherapy. In this review, we will focus on the impact of glycosylation, highlighting the role of sialic acid content.

2.2. Glycosylation in dendritic cell function: the role of sialic acid

Glycosylation, the process of adding glycans to proteins and lipids, is a fundamental cellular mechanism that affects various biological processes, including protein folding, stability, and cell signaling. Among these modifications, the terminal addition of sialic acids to glycans is critically important, as it influences cellular interactions and immune responses.

The critical position of sialic acids at the terminal end of glycans in proteins makes them important modulators, serving as biological masks and recognizable cell patterns during infection, being involved in processes such as cell-cell adhesion and signaling. Multiple studies showed the significance of sialic acids in DC function, which are depicted in Fig. 1. Specifically, surface sialic acids regulate maturation and interaction with T cells and other leukocytes. DCs exhibit significant sialyltransferase activity mainly in the endoplasmic reticulum, but also at the cell surface, which dynamically regulates their sialylation levels [18]. The pattern of sialylation changes during DC differentiation and maturation, with α2,3- α2,6- and α2,8-linked sialic acids playing distinct roles.

Immature DCs exhibit higher sialylation, particularly α2,3- and α2,6-sialylated glycoproteins, compared to mature DC, supported by significant variations in the expression of sialyltransferases and sialidases [5, 19]. Notably, *ST3Gal-I* and *ST6Gal-I* genes are upregulated during DC differentiation, correlating with increased enzymatic activity and α2,3- and α2,6-sialylation [20]. Interestingly, the neuraminidase (Neu)1 and 3 are also upregulated during DC differentiation [21]. This concurrent increase in both sialyltransferase and sialidase activity enables the dynamic regulation of cell surface sialylation, fine-tuning DC function in immune responses [22].

Maturation of DC typically increases α2,3-sialylation and decreases α2,6-sialylation, depending on the stimulus [20]. Importantly, the removal or inhibition of sialic acids from mice DC surfaces enhances their maturation, antigen presentation, and T cell activation capacity, suggesting that modulating DC sialylation is a promising approach for enhancing DC-based immunotherapies, particularly in cancer treatment [23,24]. Transcription factors like SPI-B and members of IRF family control DC differentiation and function [25]. However, it is still unknown whether they also control the expression of genes coding enzymes involved in sialylation [26–28].

2.3. Dendritic cell sialylation and endocytosis

One critical function of DC is their preparedness to endocytose pathogens via different mechanisms, such as phagocytosis and macropinocytosis, essential for DC to present peptides to T cells, in the context of MHC [29]. Sialic acids in DC significantly influence endocytosis. Desialylated human DC and ST6Gal-I and ST3Gal-I sialyltransferase-deficient DC exhibit reduced macropinocytosis but enhanced phagocytosis [30,31]. The decrease in macropinocytosis is linked to increased maturation, as DC maturation typically decreases endocytosis ability [32]. Additionally, sialidase treatment, which alters the DC cytoskeleton by reducing Rho GTPase activity, further decreases macropinocytosis. Conversely, the increase in phagocytosis after desialylation is partially because sialic acid modulates specific endocytic receptors, like Toll-like receptor-4 (TLR-4) [33,34]. Desialylation of TLR-4, facilitated by the increased expression of sialidases, such as Neu1, during DC differentiation, is crucial for activating phagocytosis [35]. Specifically, Neu1 specifically cleaves α2,3-sialic acids, unleashing TLR4/MyD88 interaction and subsequent NF-κB activation [36], modulating the production of nitric oxide and proinflammatory cytokines. Neu1 activity is initiated by LPS binding to TLR4 to potentiate G protein-coupled receptor signaling and matrix metalloproteinase-9 (MMP-9) activation [37]. These findings emphasize the intricate role of sialic acid in modulating phagocytosis and immune responses via TLR-4.

Siglecs, which bind to sialoglycans, present on both pathogens and the host, contribute to the host's innate immune response and self-recognition [38].It has been shown that sialidase treatment of DC releases Siglecs from cis ligands, allowing them to bind to glycans on other cells. Some Siglecs act as endocytic receptors aiding in the clearance of sialylated antigens. However, pathogens also express sialic-containing glycoproteins [39–42] that interfere with DC functions [43,44], altering the internalization and presentation of pathogens' antigens. Pathogens may also downregulate host sialidase activity, as observed during *Leishmania donovani* infection, to enhance Siglec interactions and downregulate TLR-4 activation pathways [45]. Or even use DCs as vectors (i.e. "Trojan horses") for infection of other immune system cells, as seen in HIV transmission via Siglec-1 [46].

These mechanisms highlight the complex role of sialic acids in modulating DC endocytosis and interactions with pathogens, thus shaping immune responses.

2.4. Dendritic cell sialylation and migration

DC migration is a key feature of the setup and regulation of immune response [47]. When responding to pro-inflammatory cytokines and pathogens, DCs undergo maturation and migrate to lymphoid tissues via lymphatic vessels to activate antigen-responsive T cells. DCs may also enter the blood, disseminate to various organs, and recirculate to dynamically maximize antigen uptake and T cell activation.

The process of DC extravasation from the bloodstream into injured or

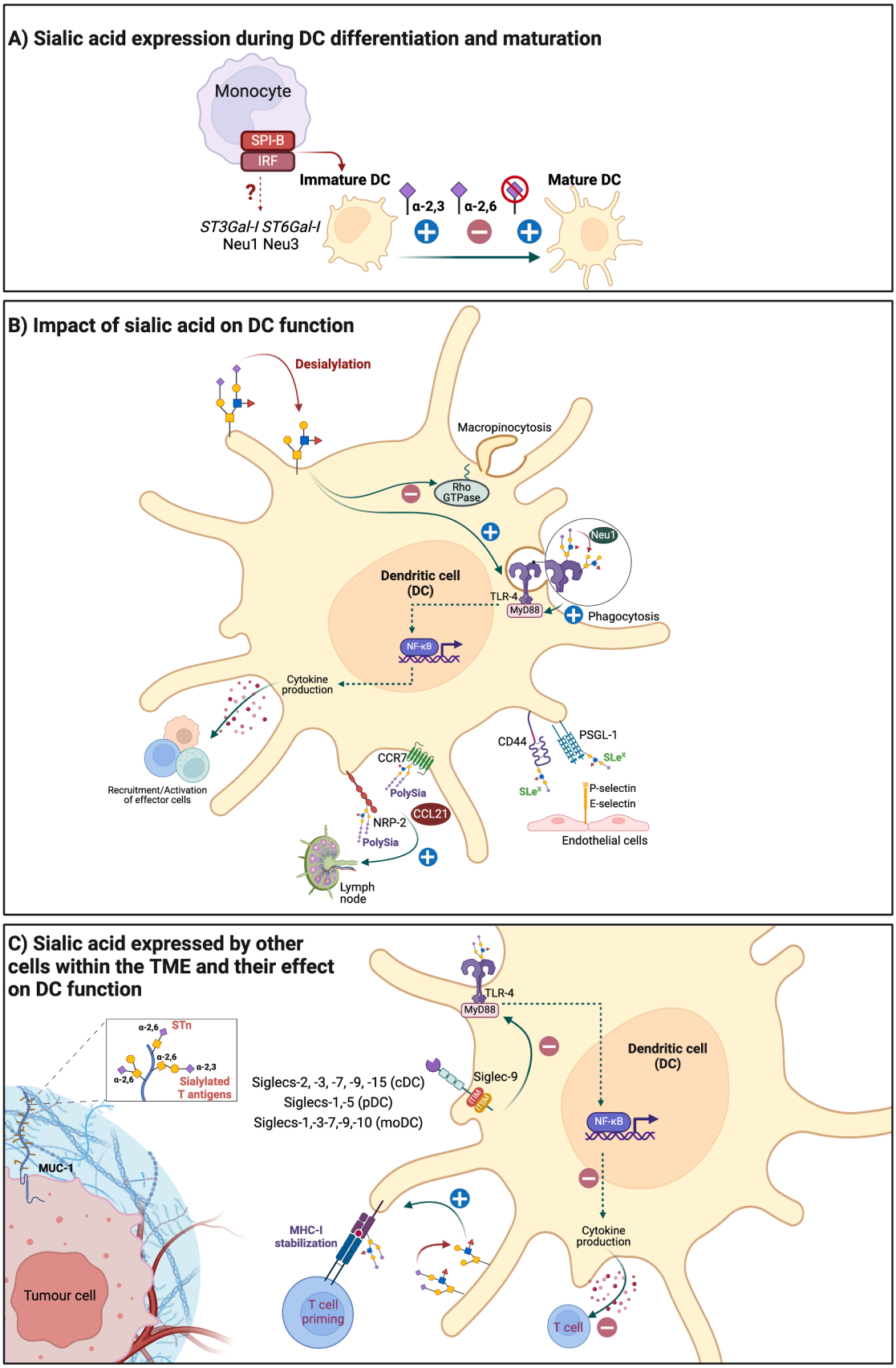

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Fig. 1. Overview of the roles of sialylation in dendritic cell function and interactions during the immune response. Sialylation is involved in dendritic cell (DC) differentiation and maturation. During differentiation, induced by transcription factors like SPI-B and IRF, DCs acquire higher levels of α2,3-sialylation. *ST3Gal-I* and *ST6Gal-I* genes together with Neu1 and Neu3 enzymes dynamically regulate sialylation, impacting DC maturation (**A**). Sialylation is crucial at regulating DC processes, including DC endocytosis and migration. Desialylated DCs show reduced macropinocytosis, and reduced Rho GTPase activity but enhanced phagocytosis, linked to altered sialic acid interactions with receptors like TLR-4. Sialic acids also regulate DC migration by influencing selectin-mediated adhesion through sLe^X decorated CD44 and PSGL1. Additionally, they modulate chemokine receptor functions, crucial for DC trafficking to lymphoid tissues (**B**). Sialylation is also key for antigen presentation. Desialylation enhances DC-T cell interactions, by improving MHC-I surface expression. Sialyloglycans from tumour cells also influence DC function through the recognition by a set of Siglecs expressed by DCs. (**C**). CCL21, C-C motif chemokine ligand 21; CCR7, C-C motif chemokine receptor 7; cDC, conventional dendritic cells; IRF, interferon regulatory factor; MHC-I, major histocompatibility complex class I; moDC, monocyte-derived dendritic cells; MUC-1, mucin-1; MyD88, Myeloid differentiation primary response 88; Neu, neuraminidase; NF-κB, nuclear factor-κB; NRP-2, neuropilin-2; pDC, plasmacytoid dendritic cells; PolySia, polysialic acid; PSGL-1, P-selectin glycoprotein ligand-1; Siglecs, sialic-acid-binding immunoglobulin-like lectins; ST3Gal-I, ST3 β-galactoside α-2,3-sialyltransferase 1; ST6Gal-I, ST6 β-galactoside α-2,6-sialyltransferase 1; STn, sialyl Tn; TLR-4, Toll-like receptor-4. Created with BioRender.com.

infected tissues is heavily dependent on interactions involving sialoglycans. Upon inflammation, endothelial cells express P- and E-selectins that bind to DC selectin ligands, namely sialyl $Lewis^x$ (sLe^X)-decorated proteins [48]. DCs express various E-selectin ligands, including the P-selectin glycoprotein ligand-1 (PSGL-1) and CD44 (HCELL) [49,50]. These sLe^X-decorated proteins, when binding to E-selectins, mediate DC rolling and tethering and subsequent transmigration over the endothelial cell surface [48]. In addition, HCELL engagement triggers VLA-4 adhesion molecule activation, enabling DC transmigration without chemokine input [49]. Other selectin ligands have been identified on different cell types, such as sLe^X decorated CD13 [51] and L1CAM [52], which have critical roles in transendothelial migration. Both CD13 and L1CAM are expressed in DCs. L1CAM is important in DC transendothelial migration due to homophilic binding [53,54]. Yet their role as DC selectin ligand and extravasation requires further investigation.

Sialic acids are also crucial in leukocyte firm arrest mediated by chemokine receptors. CCR7, the central chemokine receptor in driving DCs towards lymph nodes, binds to CCL21, depending on the ST8Sia-4-promoted polysialylation of neuropilin-2 (NRP2), which binds to the C-terminal of CCL21 [55]. Additionally, CCR7 itself is decorated with polysialic acid, which interacts with CCL21 to release CCR7 from its autoinhibited state, enhancing DC migration towards lymph nodes [56]. The ST3Gal-IV-mediated α2,3 sialylation influences CXCR2 and CCR3 chemokine-triggered firm leukocyte arrest [57,58]. Moreover, sialylated O-glycans and sulfated tyrosines in the N-terminus of CCR5 contribute to the high-affinity binding of chemokines [59].

During migration, after chemokine-triggered signalling, cells rapidly activate integrins through force-regulated conformational changes, leading to the firm arrest to the endothelium and extracellular matrix. Notably, hyposialylation of β1 integrins increases fibronectin binding and adhesion in leukocytes [60], highlighting the intricate role of sialic acid in DC migration.

Overall, DC migration is crucially modulated by specific sialylation aspects, although these mechanisms still require further elucidation. Regarding DC-based immunotherapy, most *ex vivo*-generated DCs are barely migratory and inefficient because they do not meet T cells [61]. Thus, understanding and potentially modulating DC migration through targeting sialylation pathways may improve the efficacy of these therapies.

2.5. Sialic acid moieties on antigen presentation

Sialic acids play a crucial role in modulating antigen presentation by DCs. This role of sialic acid became evident through research showing that sialic acid hindered the clustering of DCs with T cells, thus compromising antigen presentation and T cell activation [62]. Sialic acid blockade in DCs was found to facilitate high-avidity interactions with CD8+ T cells, enhancing antigen-specific responses [23].

Importantly, antigen cross-presentation, which results from complex subcellular processes that enable the processing of exogenous proteins and incorporation of resulting peptides into MHC-I is improved by sialic acid removal in human monocyte-derived DCs (MoDCs) [3]. In this way, exogenous antigens are better presented to T cytotoxic cells, which is an essential mechanism to initiate an adaptative immune cell responses against cancer.

Unlike other APCs, DCs are specialized on this special type of antigen presentation [63]. Although the effect of sialic acid on cross-presentation is not yet fully understood, further research uncovered that sialic acid removal from the human moDC surface improved the stability and surface expression of MHC-I molecules. This, in turn, enhanced DC-T cell interactions and increased IFN-γ [4], a key cytokine in immune responses. MHC-I molecules have conserved glycosylation sites, particularly on the heavy chain, where sialylation is common across different MHC-I alleles. The varying degrees of sialylation may impact peptide presentation, potentially modulating the immune response.

It has also been reported that Siglec-G regulates antigen cross-presentation of mice CD8α+DCs. The action of Siglec G expressed in phagosome resulted in excessive hydrolysis of exogenous antigens, which led to diminished formation of MHC class I-peptide complexes and hence the inhibition of cross-presentation [64].

Research into MHC-II sialylation also reveals its complex function in antigen presentation. In B cells, MHC-II antigens are susceptible to modulation by intracellular neuraminidases, suggesting that sialylation is dynamically regulated within the cell [65]. In DCs, MHC-II and invariant chains show high sialylation, which decreases upon maturation [66]. While not addressing whether MHC-II is sialylated, studies showed that sialic acid removal from DCs enhances MHC-II expression, leading to more effective T cell activation [3,4].

2.6. Sialic acid in dendritic cell-T cell activation

The primary function of DC is to interact and polarize naïve T cells towards effector or regulatory T cells, eliciting a specific, long-lasting immune response. The nature of this response is influenced by sialoglycans on DCs, which generally negatively influence T cell function.

Immature DCs and regulatory T cells express higher levels of α2,6-linked sialic acids, suggesting that this glycan motif induces immunosuppressive signaling [19]. Sialylated antigens presented by human DCs induce regulatory T cells and inhibit effector T cell function [67,68]. Conversely, blocking sialic acid synthesis or enzymatically removing sialic acids from human MoDCs enhances their maturation, activates T cells, improves CD8+ T cell responses, and upregulates pro-inflammatory Th1 profile-inducing cytokines [3,4].

Moreover, sialic acids on human DCs compete with CD80 for binding to CD28 on T cells, attenuating co-stimulation [69] necessary for full T cell activation. Another critical element in this process is the presence of disialyl core 1 O-glycan densely expressed in naïve T cells and acting as ligands of the inhibitory Siglec-7 in DCs. The expression of these ligands is controlled by the action of glycosyltransferase GCNT1 and regulates immune signalling [70].

Taken together, the sialylation of DCs has implications for T-cell interactions and impacts the balance between immunogenic and tolerogenic responses. Therefore, sialylation should be considered in fine-tuning DC-based therapy for treating various pathologies.

2.7. Siglec as sialic acid-specific lectin receptors and their role on dendritic cells

DCs express a significant range of Siglecs demonstrating its commitment to interacting with sialylated structures. cDCs express Siglecs-2, −3, −7, −9, −15, while pDCs have a more restrictive pattern and express Siglecs 1- and −5 [6]. MoDCs, frequently used as anti-cancer vaccines, express Siglecs-1, −3, −7, −9, −10. While binding sialic acid moieties, each Siglec has different preferences depending on the sialoglycan linkage (α2,3, α2,6, or α2,8), underlying glycan structure, the carrier (proteins or lipids), and modifications of sialic acids, such as acetylation or sulfation [71].

As referred to earlier, the sialic acid content on the surface of human DCs is very high, compared with other cells [21], suggesting that the *cis* interactions will have primacy over the *trans* interactions. The *cis* interactions can be released by sialidases from pathogens or by endogenous sialidases [72,73].

Siglecs likely play a largely relevant role in DC function, including host-tolerance mechanisms [20,44,74]. For example, Siglec-10 is involved in distinguishing TLR-recognized danger-associated molecular patterns (DAMPs) – generated during tissue damage – from pathogen-associated molecular patterns (PAMPs), thus controlling inflammation [75]. Moreover, Siglecs on DCs have an important role in inducing Th1 and Th2 responses, as is the case of Siglecs-1 and −7 recognizing α2,3-sialic acids and α2,8-polysialic acids, respectively. These ligands are displayed in gangliosides but also mimicked by *Campylobacter jejuni* lipooligosaccharides, which may contribute to deranged immune tolerance [76].

The recognition of sialoglycans expressed in tumour cells and stroma by Siglecs plays an important role in shaping TME and actively contributes to tumorigenesis and immune evasion [77]. For example, Siglec-9 is co-expressed with other ICs like programmed death (PD-1) on T cells in various cancers and is associated with decreased survival. Siglec-7/9 are expressed by DCs and other tumour-infiltrating leukocytes [78]. CD24, expressed in several tumours, engages with Siglec-10 on tumour-associated macrophages, blocking phagocytosis and promoting tumour evasion [79,80]. Siglec-15 is upregulated in tumour-infiltrating myeloid cells and many human cancers, suppressing T cell activity [27,78,81].

Tumour-produced mucins (MUCs) decorated with sialoglycans, found in patients' serum, engage with Siglec-9 expressed on immature DC, potentially promoting tumour escape from immunosurveillance [23,67,82]. The interaction of MUCs-1 and −16 with Siglecs on DCs masks TLR signalling, promoting an immature DC phenotype that, in turn, reduces T cell effector functions [83]. Due to the many examples of the contribution of the sialic acid-Siglec axis to T cell exhaustion and immunotherapy resistance, this axis was suggested to represent a novel IC, termed as glycoimmunecheckpoints [27].

In normal conditions, checkpoints function maintains homeostasis and controls DC activity over T cells to prevent undue activation and autoimmunity [84]. Glycosylation, particularly N-glycosylation of IC proteins, such as Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death ligand (PD-L1) is critical for their stability and function [85,86].

All in all, sialoglycans function as unique IC by engaging DC Siglecs, highlighting their role in shaping the TME and contributing to immune evasion in cancer.

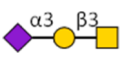
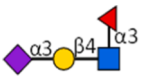
3. Mucins and sialoglycans and their relevance in immunology

Cancer cells have aberrant glycosylation patterns and display tumour-associated glycan antigens, most of them sialoglycans (Table 1), which are implicated in key pathological steps of tumour development and progression [26], hence are regarded as promising targets for anti-cancer vaccines and immunotherapy as revised by [27,28].

Table 1 presents examples of cancer-related sialylated antigens and interactions with lectins expressed in DCs. It includes, when known, the carrier, the recognizing receptor, and the consequent immunological response. Of note, we have observed a lack of comprehensive studies that bridge these interactions and their functional consequence, as most studies focus only on one end of the spectrum, often missing details about the binding partners or the immunological effects.

In cancer, hypersialylation of MUCs is a common feature, making them significant carriers of sialylated glycans such as sialyl-Tn (sTn), sialyl-T (sT), and disialyl-T (di-sT) antigens, as well as sialylated Lewis A (sLe^a) and Lewis X (sLe^x) [87]. Thus, due to their extensive glycosylation and prominent decoration with sialylated glycans, either as membrane-bound or secreted components, MUCs emerge as pivotal

Table 1
Examples of cancer-related sialoglycans and their interactions with lectins expressed in dendritic cells.

Sialoglycan	N- or O-glycan	Carrier Protein	Partner interaction	Immunological effect on DC	Reference
sialyl-Tn Neu5Acα2–6GalNAcα-O-Ser/Thr	O-glycan	MUC1	MGL	Modulation of DC phenotype and/or activity	[114]
		MUC1/CD44	not identified	Impair DC maturation and provide DCs with a tolerogenic function	[115]
		MUC1	not identified	Increase IL−10 and decrease IL−12, affecting differentiation and maturation of monocyte DCs	[116]
		MUC2	Siglec−9/3	Decrease IL−12 production on immature DCs, limiting Th1 response	[82]
sialyl-T Neu5Acα2–3 Galβ1–3GalNAcα-O-Ser/Thr	O-glycan	MUC1	Siglec−9	Reduces DC costimulation and CD8 stimulatory capacity	[90]
 **SLe^x** Neu5Acα2–3 Galβ1–4(Fucα1–3) GlcNAcβ1–3 Gal–	N-glycan	unknown	L-selectin	DC maturation	[94]
 **α2,3-sialic acid** (proposed sT)	Mainly O-glycans	proposed MUC1	Siglec−7	Upregulation of CD206, PD-L1 and immunosuppressive cytokines	[92]
α2,3-sialic acid (proposed sLe^x)	N- and O-glycans	not identified	Siglec−9		[92]

players in the in cancer immune landscape [88]. The sialylated glycans are sensed by immune cells dampening anti-tumour immune responses and hijacking the immune system for the tumour's benefit [27]. As referred in the previous sections, the Siglecs present on DCs surface are responsible for the recognition of tumour-associated hypersialylation of MUCs, and activation of immune suppressive circuits [89–92]. In the context of hypersialylation in the TME, lectins of DCs can also interact with sialoglycans present on other immune cells. An example is the case of Siglec-7 expressed on moDCs, which predominantly recognizes the disialyl-T antigen carried by CD43 mucin on T cells, regulating intra-immune signaling pathways on T cells [70].

Moreover, the O-linked glycans decorating MUC1 protein protect certain cleavage sites and hence play a crucial role in controlling its processing and presentation by DCs [93]. DCs also express other sialoglycan-binding lectins, such as L-selectin which promote DC maturation by upregulating TLR4 expression [94]. In agreement, the modification of antigens with sialic acids is an emerging strategy to regulate DCs function [68].

MUC1 interacts with Siglec-9 on DCs, probably through sT antigens, decreasing DC costimulation and CD8 stimulatory ability [89,90]. However, more recently, the interaction between Siglec-9 and sT-MUC1 was not observed in engineered cell-based arrays [63]. In this perspective, further integrative studies on the structural and functional aspects of this interaction are needed to rationalize these discrepancies.

Interestingly, emerging evidence suggests that the recognition of sialoglycans by Siglecs depends on their localization on MUC domains, particularly within the tandem repeat [89]. This indicates that the spatial arrangement and presentation of these glycans on MUCs could be critical for their interaction with Siglecs, offering new avenues for therapeutic intervention.

4. Emerging research and future directions, clinical relevance and therapeutic implications

In immunotherapy settings, DCs play a pivotal role in shaping the TME and mediating anti-tumour responses. DCs interact with T cells and can harness IC blockade therapy [95,96] and express homing factors that attract T cells to the tumours [97]. However, like for other immune cells on the TME, DC function can be impaired, and unable to activate T cells [68]. So, to maximize the therapeutic potency of the current immunotherapies it is mandatory to better understand the molecular interactions that occur between DC and T cells and their functional consequences. Interestingly, DCs represent a critical source of PD-L1 that interacts in *cis* with CD80 and perform unique roles in controlling anti-tumour cytotoxic response beyond the interaction between the PD-L1 and PD-1 [98]. The comprehension of the role of IC, such as the PD-L1, in dampening T cell activation and promoting immunosuppression in the TME led to the development of IC blockers, such as the monoclonal antibodies (mAb), which were a breakthrough in immunotherapy. However, in the clinical setting, not all treated patients respond to these therapies, indicating there are additional mechanisms impacting anti-tumour defence. Given the striking examples of immumnosupression associated with the Sialic acid-Siglec interactions, these were seen as interesting therapeutic targets and as a novel approach to boosting cancer immunotherapy or enhancing the effectiveness of existing ones [99]. One approach to improve the anti-cancer activity of myeloid cells is using blocking antibodies targeting Siglecs, which have shown promising results in preclinical studies. Several cancers display ligands for Siglec-7 and −9 (Table 1) making these receptors potential therapeutic targets, as proven by the significant reduction of tumour burden *in vivo* after administration of anti-Siglec-7 and −9 antibodies [78,100,101]. Additionally, chimeric antigen receptor (CAR) T cells based on Siglec7 and −9 were designed to promote a cytotoxic immune response toward sialoglycans, demonstrating ability to recognize tumour cells and potentiate tumour killing [102]. Based on a patient's antibody sequence, bi-specific antibodies and CART cells targeting Siglec6 were developed for chronic lymphocytic leukaemia [103,104] and anti-Siglec 3 has shown promising results on reactivation of host immunity to human hepatitis B virus [105]. Siglec-15, typically limited to myeloid cells, is aberrantly expressed by tumour cells and tumour-infiltrating myeloid cells. A monoclonal antibody targeting Siglec-15 has demonstrated success in preclinical models of lung and colorectal cancer models [80], and it is now in phase II clinical trials (NCT04699123) [106].

Evidence suggests that combinatory immunotherapy approaches targeting multiple ICs are more effective than single-target strategies. While most strategies have focused on using monoclonal antibodies to target Siglecs, only a few have addressed the control of cell surface sialoglycans.

Targeting sialic acid biosynthesis offers an alternative to direct Siglec targeting, potentially more advantageous since it blocks multiple sialic acid-Siglec interactions. Moreover, it may interfere with other sialic acid-promoted tumour properties like apoptosis, proliferation, invasion, and metastasis thus having a broader effect [107–110]. One promising approach involves the use of sialomimetics to block the expression of sialic acids in tumours [24]. This strategy demonstrated several advantages: it prevented metastatic spreading due to impaired adhesion and overall avoided tumour growth [109].

As referred to in the previous sections, in DCs, sialic acids regulate maturation and the interaction with T cells. In this context, the use of sialomimetics in mice DCs ameliorated maturation and enhanced T cell receptor-MHC-dependent and independent interactions and subsequently more robust $CD8^{+}$T cell responses [23].

The removal of sialic acids using sialidases is another promising approach. In DCs, it enhances their maturation and T cell activation capacity [3], improving immunological synapses with T cells, with a consequent significant increase in the production of IFN-γ [4]. Moreover, the interactions of the co-stimulatory molecule CD80 in DCs with its receptor-CD28 on T cells are also ameliorated by sialic acid removal [69]. These biological mechanisms account for the improved effect on anti-tumour immune response operated by T cells that were primed by desialylated human MoDCs and show that modulating DC sialylation is a promising approach for enhancing DC-based immunotherapies, particularly in cancer treatment [3,4].

The use of tumour-targeted antibody-sialidase conjugates to enhance anti-tumour immunity and halt tumour progression has shown promising results in preclinical studies [111]. In addition, Palleon Pharmaceutical is developing biological therapeutics fused with human sialidase, with E-602 related pipeline currently in phase I clinical trial. These compounds desialylate both immune cells and tumour cells, encouraging further approaches using sialidase treatments [112].

Antibodies that specifically target the aberrant sialylation patterns on tumour cells, can either set up a direct immune response against opsonized cancer cells or inhibit glycan interaction with glycan-binding proteins avoiding immune evasion. Several antibodies have shown promising in preclinical models and even entered clinical stages, where they enhance anti-tumour immunity and promote the activation of cytotoxic T cells [113]. By blocking the engagement of Siglecs, these antibodies can prevent the induction of an immunosuppressive phenotype in DCs. Furthermore, the technology of anti-sialylated glycan antibodies for cancer treatment could be adapted to target sialylated glycans expressed by immune cells. In autoimmune diseases or chronic inflammation, where sialylation of DCs may contribute to pathological immune responses, these antibodies could modulate the immune system by targeting these cells. For instance, targeting sialylated glycans on DCs or other immune cells could alter intracellular signalling and be a strategy to recalibrate immune responses, either enhancing them in the context of cancer or dampening them in autoimmune conditions.

In conclusion, the development of anti-sialylated glycan strategies represents a novel and versatile approach in immunotherapy, with potential applications not only in oncology but also in modulating immune responses in various diseases (e.g. autoimmune disorders). The ability to

specifically target aberrant glycosylation patterns on both tumor and immune cells opens new avenues for therapeutic interventions, highlighting the critical role of sialoglycans in immune regulation.

5. Conclusions

In conclusion, this review highlights the crucial role of sialylated glycans in modulating DC function and their impact on anti-tumour immunity. The sialylation of glycans on DCs significantly influences various aspects of their function, including endocytosis, migration, antigen presentation, and T cell activation. On the other hand, the recognition of sialylated MUC type glycans aberrantly expressed by cancer cells by DC surface receptors, particularly Siglecs, plays a complex role in shaping the TME, often contributing to immune evasion by tumours. Understanding these interactions provides valuable insights into the mechanisms of tumour immune evasion and opens new avenues for therapeutic strategies aimed at enhancing the efficacy of cancer immunotherapy. Targeting sialoglycans and their interactions with DCs may offer promising opportunities to improve DC-based therapies and overcome the challenges posed by the TME, ultimately leading to more effective treatments for cancer.

CRediT authorship contribution statement

Zélia Silva: Writing – review & editing, Formal analysis, Conceptualization. **Paula A. Videira:** Writing – review & editing, Supervision, Funding acquisition, Formal analysis, Conceptualization. **Filipa Marcelo:** Writing – review & editing, Supervision. **Angelina Palma:** Writing – review & editing. **Mariana Barbosa:** Writing – review & editing. **Cátia Soares:** Writing – review & editing.

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Author contributions

PAV and ZS contributed to the conception and coordination of the work. PAV, ZS, CS, MB, ASP, and FM performed the literature search and organized the data. PAV, ZS, CS, and FM wrote the original draft. All authors contributed to the writing, read, revised, and approved the final manuscript.

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