Biochemical Pharmacology 146 (2017) 23–41

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Research update

Therapeutic potential of carbohydrates as regulators of macrophage activation

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ARTICLE INFO

Article history:
Received 4 July 2017
Accepted 6 September 2017
Available online 8 September 2017

Chemical compounds cited in this article:
Chitin (PubChem CIDs: 6857375, 5288898, 70824173 & 71314665)
Chitosan (PubChem CIDs: 71853 & 21896651)
2-Deoxy Glucose (PubChem CID: 40)
β-Glucan (PubChem CIDs: 439262, 46173706 & 92024379)
Lactic acid (PubChem CID: 612)
Mannan (PubChem CID: 870)
N-acetyl neuraminic acid (PubChem CIDs: 445063 & 439197)
Sialic Acid (PubChem CID: 906)
Succinate (PubChem CID: 160419)

Keywords:
Macrophages
Carbohydrates
Polarisation
Inflammation
Immunomodulation

ABSTRACT

It is well established for a broad range of disease states, including cancer and *Mycobacterium tuberculosis* infection, that pathogenesis is bolstered by polarisation of macrophages towards an anti-inflammatory phenotype, known as M2. As these innate immune cells are relatively long-lived, their re-polarisation to pro-inflammatory, phagocytic and bactericidal "classically activated" M1 macrophages is an attractive therapeutic approach. On the other hand, there are scenarios where the resolving inflammation, wound healing and tissue remodelling properties of M2 macrophages are beneficial – for example the successful introduction of biomedical implants. Although there are numerous endogenous and exogenous factors that have an impact on the macrophage polarisation spectrum, this review will focus specifically on prominent macrophage-modulating carbohydrate motifs with a view towards highlighting structure–function relationships and therapeutic potential.

Abbreviations: 2-DG, 2-deoxy glucose; Akt, protein kinase B; ARDS, acute respiratory distress syndrome; Arg, arginase; BALF, broncho-alveolar lavage fluid; BCG, Bacillus Calmette–Guérin; CD, cluster of differentiation; cGAS, cyclic GMP-AMP synthase; COX-2, cyclooxygenase-2; DAMP, danger-associated molecular pattern; DAP12, DNAX activating protein 12 kDa; DC, dendritic cell; Dectin, DC-associated C-type lectin; DAT, di-O-acylated trehalose; DesTCR, Désiré T cell receptor; ETC, electron transport chain; EVLP, *ex vivo* lung perfusion; FcγR, Fc receptor for immunoglobulin G; Fizz1, found in inflammatory zone 1; GAG, glycosaminoglycan; GLUT1, glucose transporter 1; He3K4me3, histone H3 lysine 4 trimethylation; HIF-1α, hypoxia-inducible factor 1α; IFNγ, interferon γ; IL, interleukin; IRF, interferon regulatory factor; JAK, Janus kinase; LDH, lactate dehydrogenase; LLC, Lewis lung carcinoma; ManLAM, mannose-capped lipoarabinomannan; MCP1, monocyte chemotactic protein 1 ; M-CSFR, macrophage colony-stimulating factor receptor; Mgl, macrophage galactose-type C-type lectin; MHC, major histocompatibility complex; MHC II, MHC class II; Mincle, macrophage-inducible C-type lectin; MIP, macrophage inflammatory protein; MR, mannose receptor; Mtb, *Mycobacterium tuberculosis*; mTOR, mechanistic target of rapamycin; mTORC, mTOR complex; Neu5Ac, *N*-acetyl neuraminic acid; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; NOD2, nucleotide-binding oligomerization domain-containing protein 2; oxphos, oxidative phosphorylation; Pam3Cys, tripalmitoyl-S-glyceryl-cysteine; PAMP, pathogen-associated molecular pattern; PD-L2, programmed cell death 1 ligand 2; PGE-2, prostaglandin E2; PIM, phosphatidyl-*myo*-inositol mannosides; PLGA, poly lactic-*co*-glycolic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; PPARγ, peroxisome proliferator-activated receptor γ; PRR, pattern recognition receptor; SHP, SH2 domain-containing protein tyrosine phosphatase; Siglec, sialic acid-binding immunoglobulin-like lectin; STAT, signal transducer and activator of transcription; STING, stimulator of interferon genes; TAM, tumour associated macrophages; TAT, tri-O-acylated trehalose; TDB, trehalose-6,6-dibehenate; TDM, trehalose-6,6-dimycolate; TGFβ, transforming growth factor β; TLR, toll-like receptor; TNFα, tumour necrosis factor α; VEGFa, vascular endothelial growth factor a; Ym1, chitinase-like 3.

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http://dx.doi.org/10.1016/j.bcp.2017.09.003
0006-2952/

Contents

1. Introduction

Macrophages are mononuclear phagocytic and antigen presenting cells of the innate immune system. Due to their presence in essentially all tissues, these cells have a key role in responding to exogenous and endogenous factors, from products of tissue damage and pathogenic infections, to the introduction of biomaterials and tumorigenesis. A significant feature of macrophages is dynamic plasticity, expressed by their ability to polarise towards distinct activation states [1]. As shown in Fig. 1, the two "extremes" of these states are the "classically activated" M1 macrophages that propagate inflammation, have bactericidal activity and are highly phagocytic [1,2], and the "alternatively activated" M2 macrophages, which enhance allergic responses, resolve inflammation and induce tissue remodelling [3]. Whilst the M1 and M2 simplification is useful, it is important to bear in mind that the reality is a broad spectrum of differentiation states, continuously regulated by a myriad of signals from the microenvironment [1]. This spectrum is an argument in favour of defining macrophages based on the stimuli used to differentiate them – a system that is also regularly employed. However, in this review, the M1 and M2 extremes will be used to aid clarity. Due to their relatively long lifespan, macrophages that have attained a certain differentiation state can furthermore be re-polarised – a fundamental necessity for instance in tissue healing, and an exciting avenue for therapeutic discovery [1,4].

The current dogma suggests that M1 polarisation occurs in response to signalling downstream of cytokines such as tumour necrosis factor-α (TNFα) and interferon-γ (IFNγ) in concert with the recognition of either endogenous or exogenous danger molecules [3]. This combination induces phagocytic, antigen presenting M1 macrophages that secrete inflammatory cytokines including interleukin (IL)-1β, IL-12, IL-6, IL-23 and TNFα, as well as secretion of proteolytic enzymes and the production of reactive oxygen and nitrogen species (ROS and RNS respectively) [1,3]. These cells play key roles in protection against bacterial, fungal and viral pathogens [5]. By contrast, the cytokines IL-4, IL-13, IL-10 and transforming growth factor (TGF)β stimulate M2 differentiation [3,6]. M2 macrophages are poor antigen presenting cells that dampen inflammation, in part by secreting cytokines including IL-10 and TGFβ, promote angiogenesis and scavenge debris [1,4,7]. M2 macrophages can additionally be identified by their expression of surface markers such as the macrophage mannose receptor (MR) [8], as well as up-regulation of proteins such as chitinase-like 3-1 (Ym1), found in inflammatory zone-1 (Fizz1) and arginase (Arg) [5,9]. Whilst these established markers are convenient, macrophages can concurrently display characteristic M1 and M2 markers [10,11]. Apart from cytokines, there are numerous additional signals, including carbohydrates, that can influence macrophage polarisation towards either extreme. As macrophage responses are a key feature in cancer [12], fungal [13] and *Mycobacterium tuberculosis* [10,14] infection, as well as the successful introduction of implants [15,16], this review will primarily focus on examples of immunomodulatory carbohydrate epitopes in these clinically relevant settings.

Carbohydrates are ubiquitous in all organisms. They are prominently present on cell surfaces [17] and it is estimated that as much as 1% of the human genome is dedicated to glycosylation [18]. The human glycome is primarily built from nine monosaccharides, which may appear to limit diversity [19]. However, due to the numerous stereogenic centres, the possibility of either α- or β-linkages to any of four hydroxyl functional groups, as well as forming either linear or branched structures – as few as three different monosaccharides can construct more than 1,000 distinct trisaccharides [19,20]. Carbohydrates are thus a source of diverse information, the decoding of which is important as a means of distinguishing self from non-self, and for tailoring immune responses [21–23]. Characterising these immunomodulatory properties offers great potential for realising therapeutic applications.

2. Sialic acids mediate immunosuppressive responses

Eukaryotic cells are richly coated in sialic acids (Fig. 2): structurally diverse nine-carbon monosaccharides that are negatively charged at physiological pH [24–26]. Derived from neuraminic acid, these sugars are composed of a six-membered pyranose ring, with a three-carbon side chain and a carboxylic acid group at the anomeric position, which can be either α- or β-oriented [25,26]. Sialic acids are important for distinguishing "self" from "non-self" and are detected by sialic acid-binding proteins; prominently by sialic acid-binding immunoglobulin-like lectins (Siglecs) [24,25]. This transmembrane receptor family, of which there are 14 human and nine murine members [27], is a part of the immunoglobulin superfamily-type (I-type) lectins, which is in