Carbohydrate Research 420 (2016) 32–45

Contents lists available at ScienceDirect

Carbohydrate Research

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

Minireview

Immune sensing of microbial glycolipids and related conjugates by T cells and the pattern recognition receptors MCL and Mincle

Dylan G. M. Smith, Spencer J. Williams *

School of Chemistry and Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Parkville 3010, Australia

ARTICLE INFO

Article history:
Received 21 September 2015
Received in revised form 24 November 2015
Accepted 28 November 2015
Available online 8 December 2015

Keywords:
Glycolipids
Microbe-associated molecular patterns
Pattern recognition receptors
Cell-mediated immunity
Innate immunity

ABSTRACT

Microbes produce a wide range of small molecule glycoconjugates that constitute unique molecular signatures. These molecules are recognized by a range of detection systems, triggering immune responses to microbial pathogens and commensals. The antigen-presenting molecules of the CD1 class, CD1a-d, capture lipidic molecules and present them to diverse and innate-like T cell populations including natural killer T cells and germline-encoded mycolyl reactive T cells. The antigen-presenting molecule MR1 captures vitamin B metabolites and presents them to mucosal associated invariant T cells. In both cases, recognition of the small molecule-antigen presenting molecule complexes occurs through T cell receptors on the surface of T lymphocytes. The pattern recognition receptors macrophage C-type lectin (MCL) and macrophage inducible C-type lectin (Mincle) receptors sense glycolipids and through signalling initiate cellular activation, shaping immune responses to peptide antigens, including the differentiation of naïve T cells into conventional effector T helper cells. In this review, we provide an overview of the diverse structures of immunogenic lipidic molecules and vitamin B metabolites and their recognition by select systems of the immune system. Future advances in our understanding of the roles of such molecules in innate and adaptive immune responses will require the coordinated efforts of synthetic and natural products chemists, immunologists and biologists.

1. Introduction

Microorganisms produce a wide range of chemical signatures, which are often uniquely associated with a species or genus. An important group of microbe-specific metabolites are carbohydrate-derived small molecules including glycolipids and other glycoconjugates. The ability to sense and respond appropriately to pathogenic and commensal microbes depends on a range of sophisticated immune responses. Highly specific systems have evolved for the recognition of glycoconjugates by the immune system. Broadly, these systems can be classified into two groups. Antigen presenting molecules (APMs) are specialized proteins that are distributed throughout antigen-presenting cells, where they survey for self- and foreign lipid-like molecules (Fig. 1). Upon capture of an appropriate antigen, the resulting complex migrates to the cell surface where it is presented to T cell receptors (TCRs) on T lymphocytes (T cells). Pattern recognition receptors (PRRs) are receptors with the ability to recognize specific molecular structures, including those of altered self and commensal and pathogenic microorganisms, known variously as self-associated molecular patterns (SAMPs), damage-associated molecular patterns (DAMPs), microbe-associated molecular patterns (MAMPs), and pathogen-associated molecular patterns (PAMPs).

Cell-mediated immunity centres on the recognition of antigens presented on APMs by αβ and γδ TCRs on T cells.[1] Three major antigen-presenting systems are known. The major histocompatibility complex classes I and II (MHC-I and MHC-II) [human leukocyte antigens (HLA) in humans] are polymorphic APMs that present peptide antigens to T cells. The cluster of differentiation 1 (CD1) are a non-polymorphic group of APMs that present lipidic molecules, most notably glycolipids and peptidolipids, to diverse T cells, and a growing family of innate-like unconventional T cells.[2–4] Finally, the MHC class I-related molecule (MR1) is a monomorphic APM that binds vitamin B metabolites for presentation to the innate-like mucosal associated invariant T (MAIT) cells.[5]

C-type lectin receptors (CLRs) are an important group of PRRs. The most significant CLR for sensing of glycolipids are macrophage-inducible C-type lectin (Mincle) and macrophage C-type lectin (MCL).[6] Engagement of an appropriate glycolipid with these PRRs leads to signal transduction and cellular activation and an enhancement of immune responses through cell-mediated immunity.[7] This is of particular interest in the development of adjuvants that can boost immune responses to poorly immunogenic antigens and instruct the immune system to produce antibodies.

In this focussed minireview, we present recent advances in the occurrence, isolation and immunological effects of glycolipids and related molecules that constitute MAMPs recognized by the PRRs MCL

* Corresponding author. School of Chemistry and Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Parkville 3010, Australia. Tel.: +613 8344 2422; fax: +613 9347 5180.
E-mail address: sjwill@unimelb.edu.au (S.J. Williams).

http://dx.doi.org/10.1016/j.carres.2015.11.009
0008-6215/

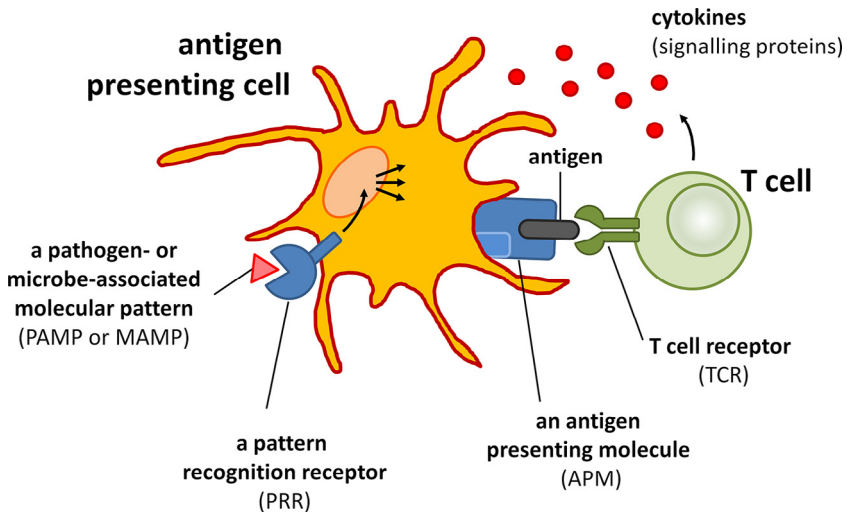

Fig. 1. Simplified schematic of glycolipid detection by antigen-presenting cells. Pathogen- or microbe-associated molecular patterns (PAMPs and MAMPs) bind to pattern recognition receptors (PRRs), leading to signalling and cellular activation. Antigens are processed and loaded into antigen presenting molecules (APMs) for presentation on the cell surface to T cells. Co-recognition of the antigen-APM complex by the T cell receptor triggers cytokine. Binding of the T cell receptor protein to the presented antigen triggers cytokine release and differentiation of T cell lineages.

and Mincle, as well as those recognized by various T cell types when presented by CD1 and MR1. We are unable to provide coverage of all glycoconjugate-detecting pattern recognition receptors. The interested reader is directed to leading reviews on a range of related C-type lectin receptors (see Refs.[7,8]), and Toll-like receptors, in particular the Toll-like receptor 4/lipopolysaccharide system (see Ref.[9]).

2. Antigen presenting systems

2.1. The CD1 system

CD1 proteins consist of five proteins that have been classified into three groups on the basis of sequence similarity.[10] Group 1 consists of CD1a, CD1b and CD1c; group 2 of CD1d; and group 3 of CD1e (Fig. 2). CD1a-d are APMs while CD1e appears to act as a lipid transfer protein that assists in the loading of CD1 molecules.[11,12] The expression of group 1 CD1 molecules are limited to CD4 and CD8 double positive thymocytes and professional antigen presenting cells, whereas the group 2 CD1d molecule has a more extensive distribution and includes non-hemotopoietic cells.[13]

CD1 proteins function to sample and monitor the lipid content of most subcellular compartments of antigen presenting cells for foreign or disease-associated lipidic molecules, and to present these molecules on the cell surface to T cells.[14] Group 1 CD1 molecules survey a wide range of microbial lipidic structures including glycolipids, lipopeptides, phospholipids, and isoprenoids.[15] The group 2 CD1 molecule CD1d surveys a narrower set of phospholipids and glycolipids, especially glycosylceramides and glycosyl diglycerides.[16,17] Group 1 and 2 CD1 molecules are characterized by antigen binding grooves that are lined with hydrophobic amino acid residues. A large number of X-ray structures are available of ligands bound to various CD1 molecules, which have revealed a common binding paradigm in which the lipid arms lodge deeply within the binding groove

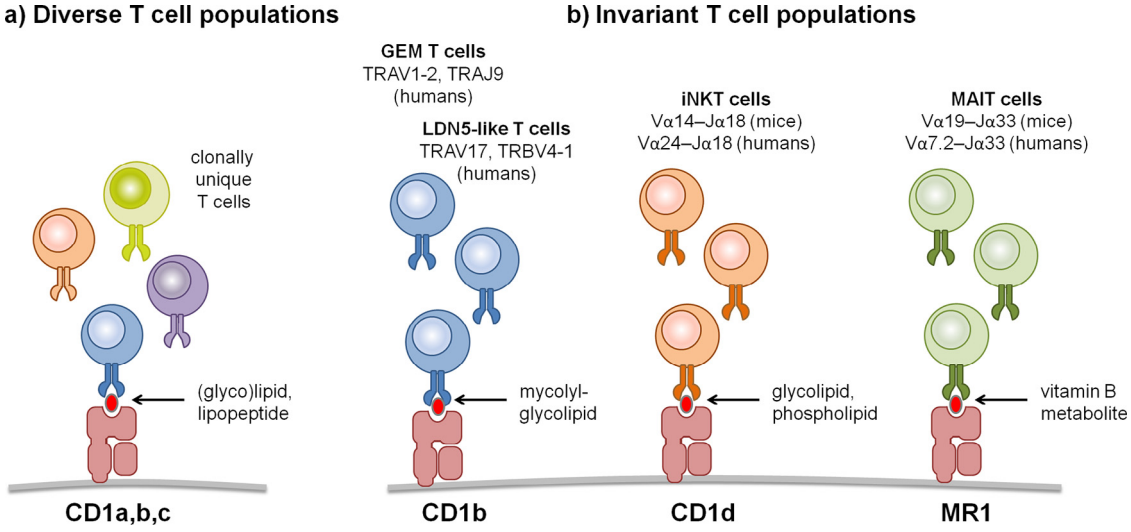

Fig. 2. Overview of CD1 and MR1 ligand presentation and recognition by (NK)T cells. a) Diverse T cell populations of clonally-unique T cell receptors recognize ligands bound to CD1a,b or c molecules. b) Certain populations of semi-invariant T cell subtypes have the ability to recognize ligands when presented by CD1b (germline-encoded mycolyl reactive (GEM) and LDN5-like T cells), CD1d (semi-invariant natural killer, iNKT cells), or MR1 (mucosal associated invariant T cells). These T cell populations are characterized by conserved or biased TCR α- and β-chains, rapid activation to effector function, and high T cell precursor frequencies.