Microbiological Research xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Microbiological Research

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

Review

Innate immune recognition of microbial cell wall components and microbial strategies to evade such recognitions

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ARTICLE INFO

Article history:
Received 2 September 2012
Received in revised form 8 February 2013
Accepted 9 February 2013
Available online xxx

Keywords:
Peptidoglycan
Nucleotide oligomerization domain protein
O-Acetylation
N-Glycolylation
N-Deacetylation

ABSTRACT

The innate immune system constitutes the first line of defence against invading microbes. The basis of this defence resides in the recognition of defined structural motifs of the microbes called "Microbial associated molecular patterns" that are absent in the host. Cell wall, the outer layer of both bacterial and fungal cells, a unique structure that is absent in the host and is recognized by the germ line encoded host receptors. Nucleotide oligomerization domain proteins, peptidoglycan recognition proteins and C-type lectins are host receptors that are involved in the recognition of bacterial cell wall (usually called peptidoglycan), whereas fungal cell wall components (N- and O-linked mannans, β-glucans etc.) are recognized by host receptors like C-type lectins (Dectin-1, Dectin-2, mannose receptor, DC-SIGN), Toll like receptors-2 and -4 (TLR-2 and TLR-4). These recognitions lead to activation of a variety of host signaling cascades and ultimate production of anti-microbial compounds including phospholipase A2, antimicrobial peptides, lysozyme, reactive oxygen and nitrogen species. These molecules act in cohort against the invading microbes to eradicate infections. Additionally pathogen recognition leads to the production of cytokines, which further activate the adaptive immune system. Both pathogenic and commensal bacteria and fungus use numerous strategies to subvert the host defence. These strategies include bacterial peptidoglycan glycan backbone modifications by *O*-acetylation, *N*-deacetylation, *N*-glycolylation and stem peptide modifications by amidation of *meso*-Diaminopimelic acid; fungal cell wall modifications by shielding the β-glucan layer with mannoproteins and α-1,3 glucan. This review focuses on the recent advances in understanding the role of bacterial and fungal cell wall in their innate immune recognition and evasion strategies.

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http://dx.doi.org/10.1016/j.micres.2013.02.005

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1. Introduction

Molecular mechanisms of host-microbial interactions are complex and difficult to understand. During infection, host immune cells recognize evolutionarily conserved microbial components called "Microbial associated molecular patterns (MAMPs)" through germline encoded pattern recognition receptors (PRRs) (Cinel and Opal, 2009; Diacovich and Gorvel, 2010; Strober et al., 2006) and activate innate defence mechanisms (Diacovich and Gorvel, 2010; Levitz, 2010; Strober et al., 2006). Over the last few years, several PRRs and MAMPs have been identified (Strober et al., 2006; Yamamoto et al., 2004). Classical examples of MAMPs are lipopolysaccharide (LPS), peptidoglycan (PG), lipoteichoic acids (LTA) and lipoproteins (LP), microbial RNA and DNA (Mogensen, 2009). The detection of MAMPs by PRRs triggers innate defense system. There are several functionally distinct classes of PRRs that recognizes microbial MAMPs. The best characterized class of PRR is Toll-like receptors (TLRs) that recognize several microbial products. 10 different types of TLRs are present in human (TLR-1–10) (Fitzner et al., 2008). Other family of PRR proteins includes Nucleotide oligomerization domain protein-1 and -2 (NOD-1 and NOD-2) (Kim et al., 2004; Le Bourhis et al., 2007; Martinon and Tschopp, 2005) subfamily, peptidoglycan receptor proteins (PGRP-1, PGRP-2, PGRP-3 and PGRP-4) (Dziarski, 2004; Steiner, 2004), Dectin-1 and -2 (Saijo and Iwakura, 2011), Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN) (Serrano-Gomez et al., 2004) and mannose receptor (MR) (Levitz, 2010), RegIII3A type lectin (Lebeer et al., 2010; Lehotzky et al., 2010) and lysozyme. Recognition of MAMPs by PRRs leads to the release of human innate defence molecules that include reactive oxygen and nitrogen species, bacteriolytic enzymes (lysozyme and phospholipase A2), antimicrobial peptides and the complement proteins (Bera et al., 2007; Fahlgren et al., 2003; Piris-Gimenez et al., 2005).

Innate immune cells recognize bacterial and fungal CW to mount an immune response. Bacterial CW is commonly called peptidoglycan (PG) or murein and is recognized by NODs, and PGLYRPs, RegIII3A, mannose binding lectin (MBL) and lysozyme. Fungal CW is recognized by TLR-2, TLR-4, Dectin-1 and Dectin-2 (Levitz, 2010). CW modifications are strategies which pathogenic and commensal microorganisms employ to evade immune recognition during colonization of the host tissue. This article will provide a brief overview about the structure, biosynthesis of bacterial and fungal CW, their recognition mechanisms by host receptors and different types of CW modifications to evade innate immune recognition.

2. Structure and biosynthesis of cell wall

The cell wall of both bacteria and fungus is a dynamic three dimensional structure that confers cellular integrity, counteracts the osmotic pressure of the cytoplasm, determines cell shape and provides protection against environmental challenges, as well as permit cell expansion during growth and cell separation after cell division.

2.1. Structure of bacterial cell wall/peptidoglycan

The cell wall of a bacterium is commonly called peptidoglycan (PG) or murein. The PG is present in all bacteria expect for mycoplasma, ureaplasma, planctomycetes, and the rickettsial agent. PG is a glycopeptide oligomer of sugars and peptides. The location and structure of PG varies between Gram positive and Gram negative bacteria. Gram positive bacterium contains thicker multilayered PG (~20–80 nm) structure surrounding the cytoplasmic membrane and accounts for the 90% of its dry weight. Gram negative bacterial PG is thinner (~10 nm); located in between the cytoplasmic membrane and the outer membrane which accounts for only 5–10% of its dry weight.

Chemically, PG is a polymer of β-(1,4)-linked *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM). The NAM is linked with short stem peptides that are cross-linked with each other to form a mesh like network around the bacterial cell. In different bacteria the average glycan chain length varies between 10 and 65 disaccharide units. The stem peptide is composed of four to five alternating L- and D-amino acids viz., L-alanine (L-Ala), D-glutamic acid (D-Glu), L-lysine (L-Lys) or *meso*-Diaminopimelic acid (*meso*-DAP) and D-alanine (D-Ala). The 3rd amino acid in the stem peptide of most Gram positive bacteria is L-Lys. *meso*-DAP is present in the 3rd amino acid of all Gram negative bacteria and in rod shaped Gram positive bacteria such as *Bacillus subtilis*, *Mycobacterium* sp and *Lactobacillus plantarum*. The 1st amino acid in the stem peptide is L-Ala which forms a lactyl bond through its N terminus to the carboxyl group of NAM. The occurrence of amino acids with alternating L- and D- configuration is a typical feature of the PG. The 3rd amino acid of the stem peptide is cross-linked with the 4th amino acid of the neighboring stem peptide by inter-peptide bridge which may or may not contain one or more additional amino acids (Fig. 1) (Royet and Dziarski, 2007; Schleifer and Kandler, 1972).

2.2. Biosynthesis of bacterial cell wall/peptidoglycan

The biosynthesis of PG is a complex process that takes place in the cytoplasm and ultimately leads to the formation of the UDP-*N*-acetylmuramic acid (UDP-NAM) covalently linked to a pentapeptide [L-Ala-D-Glu-L-Lys (or *meso*-DAP)-D-Ala-D-Ala] from UDP-NAG (uridine diphosphate-NAG) (Fig. 2). The synthesis of this UDP-NAM-pentapeptide moiety involves a superfamily of six enzymes called the Mur ligases (Mur A, B, C, D, E and F). In the next steps of PG biosynthesis, the phospho-NAM-pentapeptide moiety of UDP-NAM-pentapeptide gets transferred to the membrane acceptor, undecaprenyl phosphate. This step is catalyzed by enzyme transferase called MraY and yields lipid I. Subsequent addition of NAG with the help of enzyme MurG to the lipid I yielding the structure bactoprenol linked NAM-(-pentapeptide)-NAG known as lipid II. The lipid-II (bactoprenol linked disaccharide pentapeptide) is then transported to the outer surface of the cytoplasmic membrane where it gets incorporated into the growing PG chain through polymerization reactions catalyzed by transpeptidases and transglycosylases (Brotz et al., 1998; Gautam et al., 2011).

2.3. Structure of fungal cell wall

The structure of fungal CW differs significantly from bacterial CW or PG. While bacterial peptidoglycan is composed of glycan chains of alternating residues of NAG and NAM interspersed with

Please cite this article in press as: Sukhithasri V, et al. Innate immune recognition of microbial cell wall components and microbial strategies to evade such recognitions. Microbiol Res (2013), http://dx.doi.org/10.1016/j.micres.2013.02.005