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Review

Emerging roles of protein mannosylation in inflammation and infection

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ABSTRACT

Proteins are frequently modified by complex carbohydrates (glycans) that play central roles in maintaining the structural and functional integrity of cells and tissues in humans and lower organisms. Mannose forms an essential building block of protein glycosylation, and its functional involvement as components of larger and diverse α-mannosidic glycoepitopes in important intra- and intercellular glycoimmunological processes is gaining recognition. With a focus on the mannose-rich asparagine (*N*-linked) glycosylation type, this review summarises the increasing volume of literature covering human and non-human protein mannosylation, including their structures, biosynthesis and spatiotemporal expression. The review also covers their known interactions with specialised host and microbial mannose-recognising C-type lectin receptors (mrCLRs) and antibodies (mrAbs) during inflammation and pathogen infection. Advances in molecular mapping technologies have recently revealed novel immuno-centric mannose-terminating truncated *N*-glycans, termed paucimannosylation, on human proteins. The cellular presentation of α-mannosidic glycoepitopes on *N*-glycoproteins appears tightly regulated; α-mannose determinants are relative rare glycoepitopes in physiological extracellular environments, but may be actively secreted or leaked from cells to transmit potent signals when required. Simultaneously, our understanding of the molecular basis on the recognition of mannosidic epitopes by mrCLRs including DC-SIGN, mannose receptor, mannose binding lectin and mrAb is rapidly advancing, together with the functional implications of these interactions in facilitating an effective immune response during physiological and pathophysiological conditions. Ultimately, deciphering these complex mannose-based receptor–ligand interactions at the detailed molecular level will significantly advance our understanding of immunological disorders and infectious diseases, promoting the development of future therapeutics to improve patient clinical outcomes.

Chemical compounds studied in this article: D-Mannose (PubChem CID: 18950) Mannoseα1,3-Mannose (PubChem CID: 3476988)

Abbreviations: 3D, three-dimensional; ANCA, anti-neutrophilic cytoplasmic antibodies; APC, antigen-presenting cell; ASCA, anti-*Saccharomyces cerevisiae* antibodies; Asn, asparagine; CD, cluster of differentiation; CLR, C-type lectin receptor; CRC, colorectal cancer; CRD, carbohydrate recognition domain; Cys, cysteine; DAMP, damage-associated molecular pattern; DC, dendritic cell; DC-SIGN(R), dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (related); DCIR, dendritic cell immunoreceptor; ER, endoplasmic reticulum; FcγR, Fc gamma receptor; FcεRI, Fc epsilon receptor type 1; FL, follicular lymphoma; Fuc, fucose; FVIII, factor VIII; Gal, galactose; GalNAc, *N*-acetylgalactosamine; Glc, glucose; GlcNAc, *N*-acetylglucosamine; GPI, glycosylphosphatidylinositol; HA, hemagglutinin; HIV, human immunodeficiency virus; ITAM/ITIM, immunoreceptor tyrosine-based activating/inhibiting motif; K_d, dissociation constant; LAMP-2, lysosomal-associated membrane protein 2; LPS, lipopolysaccharide; Man, mannose; ManLAM, mannose-capped lipoarabinomannan; MASP, MBL-associated serine protease; MBL, mannose-binding lectin; mDC, myeloid dendritic cells; Mincle, macrophage inducible C-type lectin; MR, mannose receptor; mrAb, mannose-recognising antibody; mrCLR, mannose-recognising C-type lectin receptor; Mtb, *Mycobacterium tuberculosis*; NeuAc, *N*-acetylneuraminic acid; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PAMP, pathogen-associated molecular pattern; pDC, plasmacytoid dendritic cells; PRR, pattern recognition receptor; Ser, serine; SLE, systemic lupus erythromatosus; SP-A/D, surfactant protein A/D; TB, tuberculosis; Thr, threonine; TLR, toll-like receptor; UTI, urinary tract infection.

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Contents

1. Introduction

Protein glycosylation is a common post-translational modification involving the addition of complex carbohydrates (glycans) to specific amino acid residues of polypeptides. Protein glycosylation modulates important intra- and intercellular processes critical in maintaining cellular homeostasis (Ohtsubo and Marth, 2006; Varki et al., 2009) and plays central roles in protein folding and activity (Moremen et al., 2012; Xu and Ng, 2015a), in developmental processes (Haltiwanger and Lowe, 2004) and in pathogen–host interactions (Kreisman and Cobb, 2012; Venkatakrishnan et al., 2013). The normally tightly controlled glycosylation process is often dysregulated in pathologies e.g. cancer (Christiansen et al., 2014), inflammation (Scott and Patel, 2013), Alzheimer's disease (Schedin-Weiss et al., 2014), multiple sclerosis (Grigorian et al., 2012) and cystic fibrosis (Venkatakrishnan et al., 2015).

Protein glycosylation is mediated by highly specific enzymes in the cellular machinery. This "template-free" biosynthetic apparatus generates glycan structural diversity comprising different monosaccharide compositions, anomericity/linkage types (α or β) and topologies (branched or linear) that reflect the physiology of the cell at the time of biosynthesis (Rini et al., 2009). Consequently, glycoproteins commonly display extensive heterogeneity by appearing as a spectrum of closely related glycoforms (Cohen and Varki, 2010). Humans use a limited number of glycan building blocks for protein glycosylation including, but not limited to, D-α/β-mannose (Man), D-α-glucose (Glc), L-α-fucose (Fuc), D-β-galactose (Gal), D-α/β-*N*-acetylglucosamine (GlcNAc), D-α-*N*-acetylgalactosamine (GalNAc) and sialic acids e.g. D-α-*N*-acetylneuraminic acid (NeuAc) (Varki and Sharon, 2009). In particular, terminal monosaccharide residues are functionally important due to their exposed position, spatial flexibility and ability to form multivalent clusters (Cohen and Varki, 2014; Peterson et al., 2013). Glycoepitopes are recognised by two classes of receptors, glycan-binding proteins (lectins/adhesins) and glycan-binding antibodies.

Excellent reviews have summarised the important immune-modulatory roles of galactose, sialic acid and *N*-acetyllactosamine epitopes in human inflammation (Crocker et al., 2007; Johnson et al., 2013; Margreet and Geert-Jan, 2013; Rabinovich and Toscano, 2009; Schnaar, 2016). Mannose forms various α-anomeric epitopes on human and non-human glycoproteins, however, contributions of protein mannosylation to inflammatory and infection processes have received less attention. Motivated by an increasing volume of recent literature documenting the