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Review

Mucins: A biologically relevant glycan barrier in mucosal protection

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ABSTRACT

Background: The mucins found as components of mucus gel layers at mucosal surfaces throughout the body play roles in protection as part of the defensive barrier on an organ and tissue specific basis.
Scope of the review: The human MUC gene family codes up to 20 known proteins, which can be divided into secreted and membrane-associated forms each with a typical protein domain structure. The secreted mucins are adapted to cross link in order to allow formation of the extended mucin networks found in the secreted mucus gels. The membrane-associated mucins possess membrane specific domains which enable their various biological functions as part of the glycocalyx. All mucins are highly O-glycosylated and this is tissue specific and linked with specific biological functions at these locations. Mucin biology is dynamic and the processes of degradation and turnover are well integrated with biosynthesis to maintain a continuous mucosal protection against all external aggressive forces. Interaction of mucins with microflora plays an important role in normal function. Mucins are modified in a variety of diseases and this may be due to abberant mucin peptide or glycosylation.
Major conclusions: Mucins represent a family of glycoprotein having fundamental roles in mucosal protection and communication with external environment.
General significance: The review emphasises the nature of mucins as glycoproteins and their role in presenting an array of glycan structures at the mucosal cell surface.

1. Introduction

Mucosal surfaces throughout the body require protection against the variety of aggressive agents they encounter during the fulfilment of their normal function [1,2]. The mucins are an integral component in the mucus gel blanket found at these locations [3–15]. The variety of functions include gaseous exchange especially in the respiratory tree, nutrient and cofactor adsorption in the gut, transparency at the ocular surface and general roles such as lubrication, and chemical sensing. In addition, the mucosal surfaces have a close and integrated relationship to both innate and adaptive immune systems and are linked to the systemic circulation. These processes are closely related with the development of diseases at mucosal surfaces. [3,16–22]. Thus, mucosal epithelia throughout the body can be considered to be vital and dynamic entities in regular function and interaction of the body with both internal and external environments encountered on a daily basis. The airways, gastrointestinal and genitourinary tracts, the ocular surface, nasal cavity, mouth and throat are primary sites, while the cornea, cervix and upper gastrointestinal mucosa are accessed via the primary sites. As a result the mucus generated varies between each mucosal surface and requires careful investigation and characterisation in order to allow relevant study of normal and pathological functionality. Furthermore, the general mucoadhesion properties encountered at the mucosal surfaces provide a focus for drug delivery [23–39]. Recently attention has been drawn to the short term changes associated with collected mucus samples and caution is required when extrapolating results to physiological or biological situations [40].

The complexity of the protective mucosal barrier is expected due to the variety of roles and functions carried out at these locations in a continuous and dynamic manner. The normal turnover of the barrier is essential if an ongoing and viable defence is to be maintained [41–43]. This is reflected in the balance between biosynthesis, secretion and degradation. The enzymatic pathways responsible for biosynthesis and degradation are well known and in addition a range of proteins interacting with the glycan units of these glycoconjugates can be found on the CaZY website [44], illustrating the wide array of manipulations available to achieve normal, dynamic function and protection. The presence of these enzymes and proteins across the evolutionary spectrum underlines the fundamental significance of glycans in biology and stresses the need to better understand the intricacies of this system.

The main aim of this review is to present the molecular properties and functional attributes of the mucins in humans from the viewpoint of their glycobiology. This family of O-glycosylated macromolecules represent a glycoarray located on cell surfaces, the extracellular matrix and in the external environment. They have been implicated in many disease processes and a number of examples have been chosen to

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illustrate this point. We are now starting to appreciate the relevance of such glycoarrays at the biological level and recent advances have emphasised their importance [13,45–54].

2. Mucus gels, mucins and the protective mucosal barrier

The mucus layer found at mucosal surfaces throughout the body depends on the mucins or mucus glycoproteins to generate the biophysical and biochemical properties required for optimal mucosal protection. The viscoelastic, rheological and chemical properties of this group of molecules is adapted to physiological requirements dictated by the site of expression in the body. Mucins have evolved [55], leading to the family of over 20 MUC genes, which are shown in Table 1 and are found on a tissue specific basis [2,4,5,7,8,10,56–59].

The mucins are flexible macromolecular polypeptides identified by the characteristic organisation of their monomeric peptide domains (Table 2). Secreted forms appear as networks through the arrangement of monomers in homo-oligomeric structures and are mostly found at mucosal surfaces as viscoelastic gels, while the membrane-associated mucins are typical monomeric, membrane anchored glycoproteins, which do not form gels.

2.1. Secreted mucins

The oligomeric secreted mucins show a characteristic linkage of monomers through disulphide bridges located in cysteine rich, cystine knot and von Willebrand C and D domains at the N- or C-termini of the monomers. These domains flank centrally located variable number tandem repeat sequences which are unique to each MUC gene and which are also proline, threonine, serine (PTS) rich and serve to carry the glycan chains [5,60,61]. Recent work on MUC2 [60,62–65] has established the detail of the peptide domain organisation and its relation to mucin function and gel formation and is shown in Fig. 1. MUC2 has two PTS domains and shows the arrangement:***N-terminus*** von Willebrand D1, D2, D′D3, cystine rich D, *small PTS*, cystine rich D, *large PTS*, C terminal von Willebrand D4, von Willebrand B, von Willebrand C and finally cysteine knot domain ***C-terminus***.

Rapid dimerisation of the translated MUC2 peptide via the cysteine knot (CK) [62,66–68] disulphide bridges, occurs in the endoplasmic reticulum. Subsequent migration to the Golgi apparatus [62,64,68,69] enables glycosylation of the PTS domain serine and threonine residues with mucin type O-linked glycans. In the trans-Golgi network trimer formation takes place [62,64,70] and the macromolecules are concentrated in goblet cell vesicles (Fig. 2). This process is analogous to the oligomerisation and packing of von Willebrand factor and is pH and Ca^{2+} ion concentration dependent [62–64]. The creation of MUC2 trimers is necessary to permit the production of mucus networks at the cell surface and also provides a possible mechanism to account for the dramatic increase in volume seen during mucin secretion [62–64]. The sequence of events from dimerization to secretion is shown in schematic form in Fig. 2. MUC2 is arranged in bundles having an association of N-terminal trimer rings linked at right angles to dimers stabilised by C-terminal CK and von Willebrand domains. On secretion and hydration of the condensed vesicular mucus granules, stacked planar networks are formed with a volume increase of approx 3000 fold relative to the cellular granules [29,60,62–64,71]. The secreted mucins are packed in vesicles where a pH of 5.2, together with a high intragranular Ca^{2+} level is found [63].

The process of MUC5B packing [63] and release [72] is not known. The secretory vesicle pH for MUC5B is much lower than observed for the sites of mucin biosynthesis in the ER (pH 7.2) and trans-Golgi network (pH 6.0). The combination of low pH and high calcium ion concentration allow the packing of the mucin macromolecules in the vesicles and links with the remarkable volume expansion which occurs during secretion. During the process of secretion the divalent calcium ions balancing the negative charges on the mucins are exchanged for monomeric sodium ions. This doubling of counterion concentration causes an increase in osmotic pressure together with swelling of the mucin. It has been proposed that this yields the fully expanded MUC5B mucus gel on secretion [71,73,74], although this remains a controversial issue [75,76]. A role for bicarbonate in the exchange of calcium ions has been demonstrated [77–79] and linked with the CFTR channel [80]. The process of secretion is rapid, taking place in a milli-second to second period [71,74].

The time required to complete the biosynthesis of respiratory MUC5AC mucin is estimated to be approximately 2 h [72] and contrasts with the very rapid secretion and hydration processes as reported for MUC5B noted above [30].

As already implied the ability of mucins to form gels at mucosal surfaces is a crucial property which lies at the heart of the protection

Table 1
The family of mucin (MUC) genes, showing chromosomal location and PTS domain (mucin domain) tandem repeat size.

Mucin	Chromosome	Tandem repeat size (amino acids)	Main tissue expression
Secreted mucins — gel forming			
MUC2	11p15.5	23	Jejunum, ileum, colon, endometrium
MUC5AC	11p15.5	8	Respiratory tract, stomach, conjunctiva, endocervix, endometrium
MUC5B	11p15.5	29	Respiratory tract, submandibular glands, endocervix
MUC6	11p15.5	169	Stomach, ileum, gall bladder, endocervix, endometrium
MUC19	12q12	19	Evidence for MUC19 protein not reported
Secreted mucins — non-gel forming			
MUC7	4q13–q21	23	Sublingual and submandibular glands
MUC8	12q24.3	13/41	Respiratory tract, uterus, endocervix, endometrium
MUC9	1p13	15	Fallopian tubes
Membrane-associated			
MUC1	1q21	20	Breast, pancreas, duodenum, ileum, colon, trachea, bronchii, cornea, conjunctiva, fallopian tubes, uterus, endometrium, endocervix, ectocervix, vagina
MUC3A/B	7q22	17	Small intestine, colon, gall bladder
MUC4	3q29	16	Breast, respiratory tract, small intestine, colon, conjunctiva, cornea, endocervix, ectocervix, vagina, endometrium
MUC12	7q22	28	Colon, pancreas, prostate, uterus
MUC13	3q21.2	27	Colon, trachea, kidney, small intestine
MUC15	11p14.3	none	Colon, respiratory tract, small intestine, prostate
MUC16	19p13.2	156	Ovary, cornea, conjunctiva, respiratory tract, endometrium
MUC17	7q22	59	Stomach, duodenum, colon
MUC20	3q29	18	Placenta, colon, respiratory tract, prostate, liver
MUC21	6p21	15	Respiratory tract, thymus, colon