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Gel-forming mucin interactome drives mucus viscoelasticity

Bastien Demouveaux [a], Valérie Gouyer [a], Frédéric Gottrand [a], Tetsuharu Narita [b,c], Jean-Luc Desseyn [a,*]

[a] Univ. Lille, Inserm, CHU Lille, LIRIC UMR 995, F-59000 Lille, France
[b] Laboratoire Sciences et Ingénierie de la Matière Molle, PSL Research University, UPMC Univ Paris 06, ESPCI Paris, CNRS, 10 rue Vauquelin, 75231 Paris Cedex 05, France
[c] Global Station for Soft Matter, Global Institution for Collaborative Research and Education, Hokkaido University, Sapporo, Japan

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ABSTRACT

Mucus is a hydrogel that constitutes the first innate defense in all mammals. The main organic component of mucus, gel-forming mucins, forms a complex network through both reversible and irreversible interactions that drive mucus gel formation. Significant advances in the understanding of irreversible gel-forming mucins assembly have been made using recombinant protein approaches. However, little is known about the reversible interactions that may finely modulate mucus viscoelasticity, which can be characterized using rheology. This approach can be used to investigate both the nature of gel-forming mucins interactions and factors that influence hydrogel formation. This knowledge is directly relevant to the development of new drugs to modulate mucus viscoelasticity and to restore normal mucus functions in diseases such as in cystic fibrosis. The aim of the present review is to summarize the current knowledge about the relationship between the mucus protein matrix and its functions, with emphasis on mucus viscoelasticity.

Contents

* Corresponding author at: Inserm, Université de Lille, CHU Lille, LIRIC UMR 995, Faculté de Médecine, Pôle Recherche, 5ème étage, 1 place de Verdun, F-59000 Lille, France.
E-mail address: jean-luc.desseyn@inserm.fr (J.-L. Desseyn).

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1. Introduction

The aim of this review is to discuss the relationship between the structure of polymeric gel-forming mucins (GFMs) and the formation of mucus hydrogels, with a special emphasis on the viscoelastic properties. The mucus gel is a highly complex mixture of water, inorganic ions, and organic components. It protects its host from internal and external damage and therefore comprises a fundamental defensive mechanism, which is the first innate barrier to many biological organisms. The organic fraction of mucus is represented mainly by gel-forming mucins, in contrast to the membrane-bound mucins, which form the glycocalyx and make a minor contribution to gel formation [1]. For this reason we focus on GFMs in the present review. Gelation is a process driven by two GFM features: their association into large polymers and their capacity to catch and retain high water content by hydrophilic interactions using the numerous glycan chains decorating the mucin backbone, also called apomucin. In the first part of this review, we discuss the structure of human and mouse GFM, the different domains comprising the mucin backbone, their different posttranslational glycosylation modifications, which are directly related to mucus gel formation. We next discuss the composition and roles of mucus and nonmucin components in the mucus gel. We then assessed the question of how mucus acquires its viscoelastic properties and how the host organism modulates these according to the physiological context. We end by discussing mucus viscoelasticity in the context of pathology, using cystic fibrosis (CF) in the airways as an example.

2. Gel-forming mucins

2.1. Structure of the protein backbone

The five GFMs, MUC2, MUC5AC, MUC5B, MUC6, and MUC19 and their murine orthologues Muc2, Muc5ac, Muc5b, Muc6, and Muc19 display many structural similarities (Fig. 1). Four of the five GFMs are located at the same chromosomal locus (11p15.5 in humans, 7F5 in the mouse) [2–4]. It has been suggested that the GFMs evolved together and derived from a common ancestor with von Willebrand factor (vWF) [5–7]. The last GFM MUC19 is located at 12q12 (15F1 in the mouse) [8]. All GFM apomucins have a mosaic structure that is divided into three distinct regions, which are subdivided into different domains. The amino- and carboxy-terminal regions account for about one-third of the apomucin length and the central part two-thirds.

2.1.1. Amino- and carboxy-terminal regions

GFM apomucins share several similarities with the vWF from the structural viewpoint. GFMs have an amino-terminal region made of three vWF type D domains (vWD1, vWD2, and vWD3), which are rich in cysteines, and a truncated D domain (vWD′) between domains vWD2 and vWD3. All cysteine residues are highly conserved, and most are engaged in the intradomain disulfide bonds in vWF, which produces a globular secondary structure [9]. There is a greater structural diversity in the carboxy-terminal regions of GFMs, but they all contain at their carboxy extremity an ~80 amino acid (aa) cystine knot (CK) domain found in vWF and for which the three-dimensional structure was predicted to be homologous to that of transforming growth factor β, norrin, and human chorionic gonadotropin [10]. MUC2, MUC5AC, and MUC5B possess a fourth vWD domain (D4), which is followed by vWF B (vWB) and C (vWC) domains. MUC19 has only a vWC domain, and MUC6 has neither a vWB nor a vWC domain, probably because of an exon lost during evolution [6].

2.1.2. Central region

The GFM central region in the human is highly enriched in serine, threonine, and proline, and is also called the S/T/P region. This region is encoded by a single exon of several kb length, as shown for MUC5B [11]. S/T/P regions are organized mainly in tandem repeated (TR) sequences in the human, whereas the TR signature tends to disappear in lower organisms with a shorter generation time [3,6]. The high content of serine and threonine residues results in a dense *O*-glycosylation, which gives the characteristic bottle-brush structure of GFMs [11,12]. The unique size and aa sequence are features of each GFM and do not appear to have been conserved during evolution [6]. The S/T/P regions display a variable number of TR sequences between individuals and even between alleles (called VNTR polymorphism) in MUC2, MUC5AC, and MUC6 but not in MUC5B [13–16], whereas such polymorphism has not been studied in lower organisms.

The three GFMs, MUC2, MUC5AC, and MUC5B, have a central region that is interrupted by a 'naked' domain of 110 aa, which possesses 10

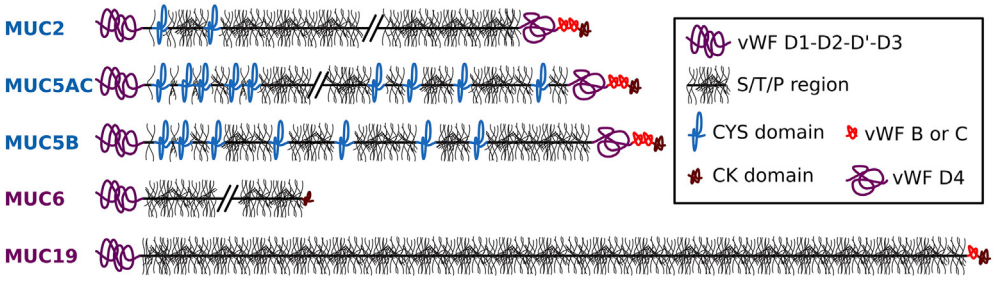

Fig. 1. GFM structure The amino-terminal region of GFM comprises vWF D1, D2, D′, and D3 domains (purple). CYS domains (in blue) are found in MUC2, MUC5AC, and MUC5B. The carboxy-terminal region comprises vWF D4 (purple), vWB and vWC (red), followed by the CK domain (brown) in GFMs with CYS domains, and only CK domain or vWF C-CK domains for GFMs without the CYS domain. Except for MUC5B and MUC19, at least one S/T/P region is subjected to VNTR polymorphism, as shown by the interruption within the apomucin. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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