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Review

The membrane-bound mucins: From cell signalling to transcriptional regulation and expression in epithelial cancers

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ABSTRACT

The membrane-bound mucins belong to an ever-increasing family of O-glycoproteins. Based on their structure and localization at the cell surface they are thought to play important biological roles in cell–cell and cell–matrix interactions, in cell signalling and in modulating biological properties of cancer cells. Among them, MUC1 and MUC4 mucins are best characterized. Their altered expression in cancer (overexpression in the respiratory, gastro-intestinal, urogenital and hepato-biliary tracts) indicates an important role for these membrane-bound mucins in tumour progression, metastasis, cancer cell resistance to chemotherapeutics drugs and as specific markers of epithelial cancer cells. Some mechanisms responsible for MUC1 and MUC4 role in tumour cell properties have been deciphered recently. However, much remains to be done in order to understand the molecular mechanisms and signalling pathways that control the expression of membrane-bound mucins during the different steps of tumour progression toward adenocarcinoma and evaluate their potential as prognostic/diagnostic markers and as therapeutic tools. In this review we focus on the molecular mechanisms and signalling pathways known to control the expression of membrane-bound mucins in cancer. We will discuss the mechanisms of regulation at the promoter level (including genetic and epigenetic modifications) that may be responsible for the mucin altered pattern of expression in epithelial cancers.

1. Introduction

Mucins belong to a heterogeneous family of large O-glycoproteins composed of a long peptidic chain called apomucin on which are linked hundreds of oligosaccharidic chains. Based on biochemical studies, mucins were initially defined as high-molecular weight (MW) molecules secreted by epithelia, able to form viscoelastic gels and responsible for rheological properties of mucus. Advent of molecular biology in the nineties allowed identification of high MW O-glycoproteins with structural characteristics of mucins which contained a transmembrane (TM) domain. Today, the family of membrane-bound mucins includes MUC1, MUC3A/B, MUC4, MUC12, MUC13, MUC15, MUC16, MUC17, MUC20 and MUC21 [1]. Among them, MUC1 and MUC4 are best characterized. Based on their structure and localization they are thought to play important biological roles in cell–cell and cell-extracellular matrix interactions, in cell signalling and in biological properties of cancer cells [2–6]. Moreover, their specific pattern of expression during the different steps of tumour progression toward adenocarcinoma suggests that they play important roles in tumourigenesis and that they are specific markers of epithelial cancer cells. For all these reasons, membrane-bound mucins stay under intense investigation as both potent new biomarkers and therapeutic targets in epithelial cancers. On another hand, the family of secreted mucins, gel-forming components of viscoelastic mucus gels protecting the epithelia, includes mucins MUC2, MUC5AC, MUC5B, MUC6, and MUC19 [7]. Their main function is to participate in mucus formation by forming a tridimensional network *via* oligomerization domains to protect underlying epithelia against various injuries (inflammation, bacteria, virus, pollutants, pH, etc). MUC7 and MUC9 are smaller secreted mucins that do not oligomerize [8,9].

A better understanding of the molecular structure of regulatory regions as well as mechanisms governing mucin expression is also mandatory if one wants to assign direct roles to mucins in carcinogenesis and better understand their influence on the biological properties of the tumour cell. Studies aiming at deciphering the signalling pathways will allow identification of potential therapeutic targets with the ultimate goal to restore normal mucin expression at the cell surface. Moreover the use of mucin promoters in gene-based therapy is under investigation and may provide new biological tools [2]. Animal models will also help define *in vivo* the

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roles of membrane-bound mucins in pathophysiological situations and help the scientific community determine whether mucin altered expression is a consequence of epithelium alteration or actively contributes to histological changes that promote carcinogenesis.

2. MUC1 and MUC4 have a cell- and tissue-specific pattern of expression

In this part of the review we will only describe the pattern of expression of membrane-bound mucins (Table 1). For expression of secreted mucins in the same cancers, see excellent following reviews [10–12].

2.1. Respiratory tract

The mucin gene expression pattern in normal airways and lung is complex [13]. Mucin genes are expressed in an array of epithelial cells exhibiting various phenotypes: *MUC1* in submucosal glands and *MUC1*, *MUC4*, and *MUC13* in the surface epithelium. In distal bronchioles, Clara cells express *MUC1* and *MUC4*. The alveolar type II epithelial cells express the MUC1 glycoprotein whereas *MUC4* gene expression is not detected in normal type II pneumocytes but is found in type II pneumocyte hyperplasia [13].

In atypical adenomatous hyperplasia (AAH), the preinvasive lesion of peripheral lung adenocarcinomas, high level of MUC1 expression and very low levels of other mucins have been shown by immunohistochemistry (IHC) (Table 1). MUC1 expression was significantly decreased in the progression from AAH through nonmucinous bronchioloalveolar carcinoma (BAC) to invasive adenocarcinoma while depolarized MUC1 was significantly increased [14].

In hyperplasia (basal cell/goblet cell), metaplasia and dysplasia, the pattern of qualitative expression of mucin genes is similar to that determined for normal mucosae. Nevertheless quantitative variations of *MUC4* expression levels are observed. No expression of *MUC3* is found in squamous lesions as in the normal respiratory surface epithelium [15].

Lung cancers are largely classified into two major groups based on their histopathologic differences: non-small-cell lung cancer (NSCLC), which is further divided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma; and small-cell lung carcinoma. The recent studies on mucin expression in lung cancer have been conducted to establish a relationship between the expression of any particular mucin and the histologic subtype [10,15–17]. Lung adenocarcinomas express mucin mRNAs which are expressed in normal respiratory mucosa (*MUC1, MUC4*) and *MUC3* mRNAs which are not detected in normal lung by *in situ* hybridization (ISH) [16]. Nonmucinous type of BAC and non BAC type adenocarcinomas share the constant expression of *MUC1* and *MUC4*, and variable expression of *MUC3* [16,18]. Among adenocarcinomas, the mucinous type of BAC (m-BAC) has a particular pattern of mucin gene expression since all mucin genes are expressed. Coexpression of *MUC1* and *MUC3* is constant. Coexpression of *MUC4* is very frequent. This complex but homogeneous expression pattern in m-BAC is in agreement with the great cellular homogeneity of this type of adenocarcinoma [16,18].

2.2. Gastro-intestinal tract

2.2.1. Oesophagus

The normal oesophageal epithelium is considered as nonmucus-secreting. MUC1 and MUC4 are the main mucins expressed both at the mRNA and protein levels in the stratified squamous epithelium [19,20]. Recently, expression of the membrane-bound mucin *MUC20* has also been found, without any precision concerning staining location [21].

Table 1
Expression pattern of the membrane-bound mucins MUC1, MUC3 and MUC4 in normal, premalignant and malignant epithelia. + = expressed; ++/+++ = overexpressed; ↓ = decrease of expression. All data presented are at the protein level unless RT-PCR or *in situ* hybridization (ISH) is indicated.

	Normal	Metaplasia/Hyperplasia/Dysplasia	Cancer
Lung	Surface epithelial cells MUC1+, MUC4+(ISH) Submucosal gland MUC1+(ISH) Clara cells MUC1+, MUC4+ Alveolar type II MUC1+	Atypical adenomatous hyperplasia (AAH) MUC1+++	Lung adenocarcinoma MUC1+, MUC4+ Nonmucinous bronchioloalveolar carcinoma (BAC) MUC1↓, MUC4+
Oesophagus	Squamous epithelial cells MUC1+, MUC4+	Barrett's oesophagus MUC4↓, MUC1 n.d. (conflicting reports)	Squamous cell cancer MUC1+, MUC4+ Adenocarcinoma MUC1+++ (conflicting reports), MUC4+++
Stomach	MUC1+	Intestinal metaplasia; MUC1↓ (good prognosis), MUC3+++ (bad prognosis)	
Small intestine	Brünner's gland MUC1+, MUC4+ Duodenum MUC1+ (RT-PCR) Columnar cells MUC4+ Vater's ampulla MUC1+, MUC4+		Small intestine adenocarcinoma MUC1+++ (poor differentiation) Ampullary adenocarcinoma MUC1+++ (poor prognosis)
Colon	Columnar cells MUC4+ Goblet cells MUC4+	Low-grade dysplasia MUC3+++ (early stage marker)	Adenocarcinoma MUC1+++ (late stage marker), MUC4↓
Pancreas	Ductal cells MUC1+	Pancreatic intraepithelial neoplasia; PanIN1A MUC1++, MUC4+; PanIN3 MUC1++; MUC4++ Intraductal papillary mucinous neoplasm MUC1+++ (bad prognosis)	Adenocarcinoma MUC1+++, MUC4+++
Hepatobiliary tract	MUC1 weak, MUC3+++		Gallbladder carcinoma MUC1+ Cholangiocarcinoma MUC1+, MUC4+ Intrahepatic cholangiocarcinoma (ICC) MUC1++