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Pseudomyxoma Peritonei: Uninvited Goblet Cells, Ectopic MUC2

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Abstract

Pseudomyxoma peritonei (PMP) is a challenging clinical syndrome characterized by multifocal peritoneal collections of extracellular mucins. Mucins are high molecular weight, heavily glycosylated proteins differentially expressed by various types of epithelial cells. In this pathological condition, goblet cells originating from a mucinous tumor of the appendix gain access to the peritoneal cavity where they secrete mucin ectopically. Secreted mucin thus accumulates and forms the characteristic feature of the disease. Therefore, goblet cells and secreted mucins constitute the two key elements of the disease. MUC2 is the PMP's specific, predominant mucin. It is a highly viscous, gel-forming mucin that accounts for the characteristic appearance of PMP mucinous deposits as compared to the mucinous implants of ovarian origin. Mucin deposits are the real cause of PMP's morbid complications irrespective of the site of origin, the mechanism of peritoneal spread, or the level of neoplastic transformation. In this article, role of mucin in gastrointestinal physiology and PMP pathology are reviewed and the potential of MUC2 as a therapeutic target are discussed.

Keywords: Pseudomyxoma peritonei; PMP; Mucin; Goblet cells; MUC2

Introduction

Mucosal surfaces throughout the body are coated by a mucus layer. Mucus is a slimy, viscoelastic secretion which serves as a protective barrier against harmful substances and acts as a lubricant between the lumen and the cell surface. The most abundant constituents of mucus are mucins. Also termed MUC glycoproteins, mucins are a diverse family of high molecular weight, heavily glycosylated proteins which are differentially expressed by various types of epithelial cells in a relatively organ- and cell type-specific manner [1]. To date, over 20 different *MUC* genes have been identified which encode the protein backbone of mucins (Table 1) [2]. MUC glycoproteins are categorized into *membrane-associated* as well as *secreted* mucins, with the latter being subdivided into *gel-forming* and *non-gel-forming* types [3,4].

MUC1 is the best-characterized membrane-associated mucin. It consists of an extracellular region (ectodomain), a transmembrane domain, and a cytoplasmic, signaling tail and is expressed on the apical surface of most epithelial cells [5,6]. Membrane-associated mucins establish the molecular composition of the cell surface, communicate information about extracellular status as receptors or sensors of the environment and mediate intracellular signal transduction [7]. They also play an important role in the renewal and differentiation of the epithelium, cell adhesion and immune response [2]. Near the cell surface, the membrane-associated mucin layer might be in contact through interactions with the secreted mucins, contributing to physicochemical protection of the epithelial cell surface from adverse conditions.

Secreted mucins, on the other hand, are synthesized and secreted by specialized epithelial cells at the mucosal surfaces of digestive, respiratory and reproductive tracts by the secretory epithelia of the liver, pancreas, gall bladder, kidney, salivary glands, lacrimal glands and eye [8]. MUC2, a characteristic secreted mucin which participates in the formation of extracellular gels, is a site-specific mucin synthesized by the intestinal goblet cells [2].

At the gastrointestinal (GI) tract, mucins form part of a dynamic, interactive defense system active at the mucosal surface. Structural characteristics and integrity of the mucus layer play an essential role in physiological function of this integrated innate and adaptive immunity [9].

Qualitative and/or quantitative abnormalities of Goblet cell-secreted mucins have been implicated in various GI disorders, including inflammatory and neoplastic diseases [10,11]. Among these, of particular interest in our research group, is pseudomyxoma peritonei (PMP), a rare clinical syndrome the characteristic feature of which is the progressive accumulation of mucin in the peritoneal cavity. In this article, biology of intestinal mucins in health and PMP disease is reviewed and potential of MUC2 as a therapeutic target is discussed.

Physiology of Intestinal Mucins

Goblet cells and GI mucus

The GI tract is a complex ecosystem generated by the alliance of the epithelial cells, immune cells and resident microbiota. A balanced, dynamic interaction among these components is essential for the maintenance of intestinal homeostasis and the normal function and activity of digestive system [12]. The GI epithelium in association with the overlying mucus layer acts as a barrier that protects the internal milieu against potential physical and chemical hazards in the harsh luminal environment [13]. Mucus in stomach and colon is composed of two layers. The outer, loose layer is the habitat of the commensal flora and is degraded by the commensal flora that finally degrades and associates with intestinal contents. The inner, dense layer is firmly attached to the epithelium and is free from bacterial colonization. Thus, bacteria normally do not reach the epithelial cells and are well separated from the immune system [14]. Mucus is generally composed of mucins, water, inorganic salts, immunoglobulins and secreted proteins. As the main product of goblet cells and the major component of mucus, secreted mucins account for most of biochemical and biophysical properties of mucus. They not only facilitate the transit of intestinal contents [15], but also participate in the front line of the enteric host defense [16]. The GI secreted mucins primarily function as a protective gel barrier between the underlying epithelium and the

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Type of mucin	Designation	Site of expression
Membrane-associated	MUC1	Almost all glandular epithelial surfaces of respiratory, female reproductive and gastrointestinal tracts, middle ear, salivary gland, mammary gland and normal pancreatic intralobular ducts
	MUC3A	Gastrointestinal epithelia
	MUC3B	Gastrointestinal epithelia
	MUC4	Respiratory tract, salivary glands, stomach, colon, eye, vagina, ectocervix, uterus, and prostate
	MUC11	Gastrointestinal, respiratory, reproductive and urinary tracts, liver and thymus
	MUC12	Colon, stomach, pancreas, prostate, and uterus
	MUC13	Gastrointestinal and respiratory tracts, middle ear, and kidney
	MUC15	Placenta, salivary gland, thyroid gland, trachea, esophagus, kidney and testis
	MUC16	Ocular surface, respiratory and female reproductive tract epithelia and middle ear
	MUC17	Gastrointestinal tract, fetal kidney, and conjuctival epithelium
	MUC20	Kidney, placenta, lung, prostate, liver, colon, esophagus, rectum and middle ear
	MUC21	Respiratory tract, thymus, colon, and testis
Secreted gel-forming	MUC2	Goblet cells of small intestine and colon
	MUC5AC	Tracheobronchial goblet cells, gastric epithelial cells, conjunctiva and lacrimal glands
	MUC5B	Salivary glands, tracheobronchial and esophageal epithelia, pancreatobiliary and endocervical epithelia
	MUC6	Gastric mucosa, duodenal Brunner's glands, hepatobiliary tract, pancreatic centroacinar cells and duct, basal endometrial and endocervical glands
Secreted non-gel-forming	MUC19	Salivary glands, submucosal gland of the tracheal tissue, corneal and conjunctival epithelia, and lacrimal gland tissue
	MUC7	Epithelium of the oral cavity, minor salivary gland, respiratory tract , submucosal glands of the bronchus, conjunctivae and pancreas
	MUC8	Normal human Nasal epithelial (NHNE) cells and middle ear epithelium
	MUC9	Fallopian tubes (non-ciliated oviductal epithelial cells)

Table 1: Classification of mucin family.

lumen. Similar to the cell surface receptors, the oligosaccharide chains of the mucins bind and trap microorganisms and prevent them from accessing the mucosal surface [17].

Goblet cells, together with absorptive enterocytes, Paneth cells and enteroendocrine cells, comprise the four principal differentiated cell types of the intestinal mucosal epithelia, all of which arise from a multipotent stem cell located near the base of the mucosal crypts [18]. Both absorptive enterocytes and intestinal goblet cells express a variety of membrane-associated mucins with structural similarity, including MUC1, MUC3, MUC4, MUC12, MUC13, and MUC17. Goblet cells, in addition, are the specific source of secretory MUC2 and MUC5AC. Goblet cells are morphologically characterized by the distended theca containing the mucin granules located below the apical membrane. Along with an increase in the number of commensal microorganisms, the proportion of goblet cells among intestinal epithelial cell types increases caudally from duodenum (4%) to distal colon (16%) [19]. Goblet cells synthesize and secrete such bioactive components of mucus as secreted mucins, trefoil peptides [20], resistin-like molecule β (RELMβ) [21], and Fc-γ binding protein (Fcgbp) [22]. Two secretory mechanisms are employed by goblet cells: constitutive (or basal) secretion, which is low-level, continuous secretion depending on cytoskeletal movement of secretory granules, and stimulated (or regulated) secretion, which involves exocytosis of granules in response to external stimuli [23].

MUC2 is specifically expressed by goblet cells of the small intestine and colon. It is the substantial component of the two layers of intestinal mucus. MUC2 is released and expanded in volume to form the inner mucus layer from bottom. It is then transported and converted to the outer loose mucus layer at a sharp border and then expanded in volume in the outer loose mucus layer, where it is finally dissolved by bacterial enzymes and transported away with the fecal stream. This mucus bilayer is organized by proteolytic cleavage of MUC2. The more densely packed inner layer attached to the epithelium is comprised of uncleaved MUC2. Therefore, loss of MUC2 confers a microenvironment in which bacteria can activate an inflammatory response at the epithelial surface [14,24].

Structure, synthesis and degradation of MUC2

MUC2 was the first human secreted mucin to be identified and characterized [25,26]. *MUC2* gene is clustered with *MUC5AC, MUC5B, and MUC6* genes on chromosome 11p15.5 [27]. Accordingly, MUC2 shares structural and physicochemical features with MUC5AC, MUC5B and MUC6 which are expressed in gastric and respiratory glandular epithelium. As illustrated in Figure 1, MUC2 core protein has more than 5100 amino acids and consists of 5 different regions. There are two central repetitive regions rich in potential O-glycosylation sites, to which branched carbohydrate chains of 4-12 sugars are O-glycosidically linked to form a closely packed sheath around the central protein core. The first region, also known as VNTR domain, is a large domain that contains 50-100 "variable number of tandem repeats (VNTRs)" of 23 amino acids, in particular, threonine. The second repetitive region, also called PTS domain, is a 347 amino acid domain, containing irregular repeats rich in proline, threonine and serine. These two highly glycosylated segments are linked together by a 148 amino acid, cysteine containing segment. On their lateral sides, too, VNTR and PTS domains are flanked, respectively, by a 984 amino acid, C-terminal domain and a 1400 amino acid, N-terminal domain, both of which are rich in cysteine. These regions are the presumed sites for end to end polymerisation of mucin subunits to form the linear native polymeric mucin molecule. Within C- and N-terminal regions, MUC2 monomer also contains four cysteine rich D-domains with sequence homology to von Willebrand platelet aggregating factor (vWF), of which three (D1-D3) exist within the N-terminal region and one (D4) resides in the C-terminal region.

In the N-terminal region, MUC2 also contains a putative disulphide isomerase activity sequence as well as a signal sequence. The C-terminal region contains a cysteine knot of 11 conserved cysteine residues and a heparin binding site sequence. Moreover, 31 potential N-glycosylation sites (oligosaccharide chains with mannose core N-glycosidically linked to asparagine) are present in MUC2. Of these N-glycosylation sites, 10 and 18 sites are located in the N-terminal and C-terminal regions, respectively, and three are found in the 148 amino acid region between VNTR and PTS domains [24,28].

The first stage in the biosynthesis of MUC2 is the formation of MUC2 monomer as an N-glycosylated apoprotein, O-glycosylated with just galNAc, in the endoplasmic reticulum. Subsequently, MUC2 dimers form when intermolecular disulfide bonds bridge between the C-terminal cysteine knot domains. During transit through the Golgi apparatus, MUC2 dimers become heavily O-glycosylated. Complete glycosylation of the dimers occurs in the Golgi where trimerization through disulfide bonds at the N-terminus forms protease-resistant trimers. The fully glycosylated and processed MUC2 mucin is densely packed and stored in secretory granules/vesicles and released by the two pathways described earlier (Figure 2). Massive secretion of MUC2 mucin by exocytosis in stimulated secretion is triggered by a wide array of bioactive factors, including cholinergic agonist, hormones (neuropeptides), microbes and microbial products and toxins, inflammatory cytokines, and reactive oxygen and nitrogen species. These mucin secretagogues signal via secondary messengers such as intracellular Ca^{2+}, cyclic adenosine monophosphate (cAMP), and diacylglycerol that activates protein kinase [19].

The degradation of gastrointestinal mucins is complex. GI proteases slowly dissolve the adherent mucus gel throughout the gut. This results in the release of highly glycosylated mucin fragments that are resistant to further proteolytic degradation. Enzymatic breakdown of the oligosaccharide chains of the highly glycosylated mucin fragments,

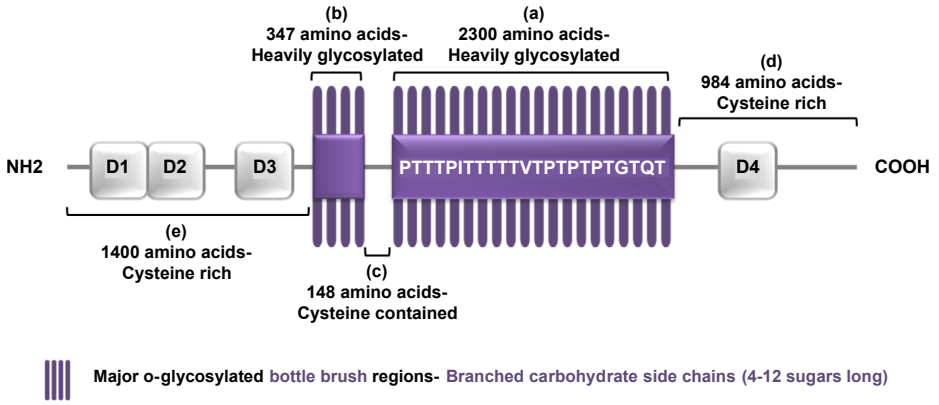

Figure 1: Schematic representation of the MUC2 gene product. The protein core consists of five different regions. Segment (a) and (b) are two central repetitive regions rich in potential O-glycosylation sites, to which branched carbohydrate chains of 4-12 sugars are O-glycosidically linked to form a closely packed sheath around the central protein core. Segment (a), also known as VNTR domain, is a large domain that contains 50-100 "variable number of tandem repeats (VNTRs)" of 23 amino acids, in particular, threonine. Segment (b), also called PTS domain, is a 347 amino acid domain, containing irregular repeats rich in proline, threonine and serine .These two segments are linked together by segment (c) a 148 amino acid, cysteine containing region. Segments (d) and (e) are extensive peptide chains rich in cysteine located at the C and N terminal ends, respectively. They contain D domains which have sequence homology to the von Willebrand factor. These regions are the presumed sites for end to end polymerisation of mucin subunits to form the linear native polymeric mucin molecule.

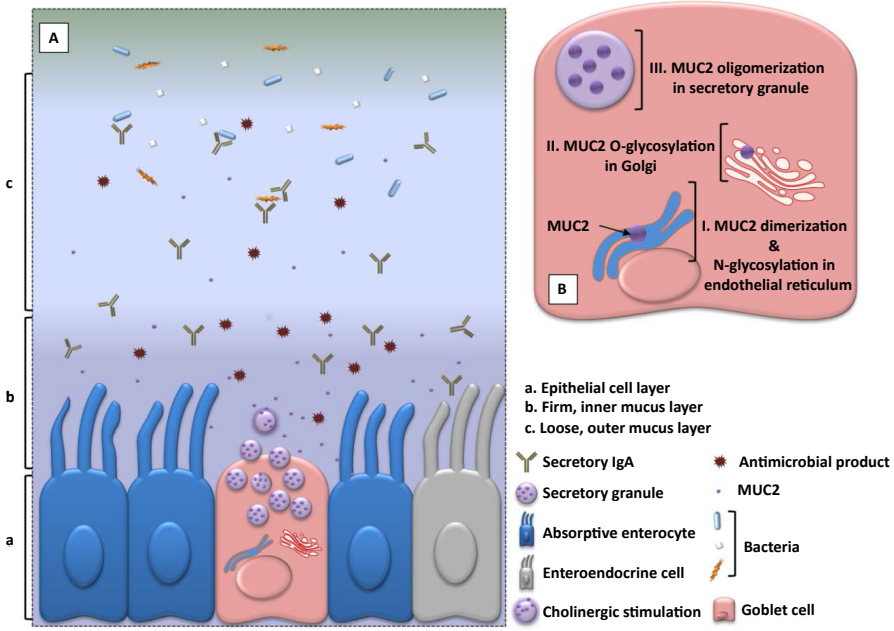

Figure 2: A schematic representation of two mucus layers overlying the epithelial cell surface of colon. Colonic epithelial cell surface is covered by an inner, firmly attached layer surrounded by an outer, loosely adherent layer. This mucus coating is largely made of a MUC2 mucin network produced by the goblet cells, combined with other host defense molecules produced by goblet cells, enteroendocrine cells and absorptive enterocytes. Microorganisms are associated with the outer, but not the inner, layer.

mediated by the gut microflora, occurs only in the colon. Finally, the remnant protein core, deglycosylated and exposed to colonic proteases, undergoes hydrolysis [28].

Pseudomyxoma Peritonei

Pseudomyxoma peritonei (PMP) is a clinical syndrome characterized by accumulation of grossly evident mucin within the peritoneal cavity as well as mucinous implants on the peritoneal surfaces and omentum. The incidence of the disease is estimated 1 per million per year, with a peak incidence in the 5th decade of life [29,30]. The earliest description of the condition was by Weaver [31]. Later in 1884, Werth introduced the term "pseudomyxoma peritonei" when describing the syndrome in association with an ovarian mucinous tumor [32]. In patients with PMP, organizing pools of mucin gradually form within the peritoneal fat or on the serosal surfaces of the viscera. The progressive collection of viscous, gelatinous material with no place of drainage gives rise to the characteristic appearance of jelly belly [33]. PMP is microscopically characterized by large, relatively acellular or cellular mucin aggregates, the latter of which may be presented as mucin aggregates containing strips of mucinous epithelium, mucinous epithelium encircling glands and cysts, or clusters of mucinous epithelium lying within mucin pools [34].

Etiology and classification of PMP

Initial reports described PMP as a syndrome in association with an ovarian tumor [32], or an appendiceal mucocele [35]. Since then, the controversy has been surrounding PMP's entity and origin, hence lack of a coherent classification [36]. The term PMP has been used by many clinicians to describe any condition leading to extensive intraperitoneal accumulation of mucin, thus incorporating mucinous tumors of different origins, in particular the appendix and ovaries, with different levels of neoplastic transformation. As this ambiguity has resulted in ongoing confusion in both differential diagnosis of the disease and optimal care of the patients [37], many scholars have attempted in their investigations to minimize uncertainty over the etiology of the disease and/or to offer a unified classification for PMP.

Despite the debates, a consensus has been reached throughout the past two decades [38-43] that PMP originates from an appendiceal mucinous tumor, which may or may not have been diagnosed earlier, and that ovaries are secondarily involved in PMP. Moreover, a number of studies strongly suggest that PMP is a generally low-grade neoplastic process, where extraperitoneal metastases and solid organ involvement are uncommon. [36]. According to a clinicopathological classification suggested by Ronnett et al. [44], PMP cases are categorized into three groups. These include a benign category termed disseminated peritoneal adenomucinosis (DPAM), a malignant group called peritoneal mucinous carcinomatosis (PMCA) and a third, hybrid category named peritoneal mucinous carcinomatosis with intermediate or discordant features (PMCA I/D), also known as intermediate features group (IFG). Soon after, however, Sugarbaker et al. and Ronnett et al. [45,46] suggested a more restricted definition with PMP just including benign peritoneal tumors with copious mucin secretion arising from primary appendiceal mucinous adenomas (disseminated peritoneal adenomucinosis or DPAM) with a significantly more favourable prognosis. As follows, this notion has been challenged by O'Connell et al. [42] who described mucin production as a process independent of malignant transformation of goblet cells.

Pathogenesis of PMP

Under normal conditions, mucin is constitutively expressed by the goblet cells and secreted into the intestinal lumen where it eventually degrades and washes away in the fecal stream. In PMP, however, it is believed that appendiceal goblet cells gain access to the peritoneal cavity where they produce ectopic mucin that is unable to drain away [45-47]. In brief, goblet cells arising from a primary mucinous tumor of the appendix grow and proliferate. With the appendiceal lumen being obstructed and mucus being trapped inside, the appendix becomes distended and an appendiceal mucocele subsequently develops. As intraluminal pressure rises, either a small perforation of the appendiceal wall or blow-out of the mucocele releases mucus and tumor cells into the peritoneal cavity. This event is considered as the initial step and the key incident towards development of the clinical syndrome of PMP. Although the perforation of the appendix may become resealed and invisible, indolent free or intraperitoneally seeded tumor cells continue to proliferate for months or even years and produce a large amount of mucin with no place to drain. This eventually gives rise to the characteristic manifestation of PMP as locoregional dissemination of tumor implants and mucin deposits throughout the peritoneal cavity.

As compared to nonmucinous metastases from primary cancers, PMP displays a unique pattern of peritoneal dissemination. This pattern forms according to a redistribution phenomenon that complies with adhesive properties of the tumor cells, intraperitoneal fluid reabsorption pathway, and, gravity [47]. Mucinous epithelial tumor cells do not have adhesion molecules exposed on the cell surface. This lack of "stickiness" means that the tumor cell will not actively attach to an abdominal or pelvic surface. Instead, the exfoliated tumor cells and their mucinous product will be passively circulated by the peritoneal fluid current and deposited at the sites of the peritoneal fluid reabsorption (inferior surface of the right hemidiaphragm as well as the greater and lesser omentum) and, by gravity, within the dependent portions of the peritoneal cavity (such as the rectovesical pouch, the right retrohepatic space and the paracolic gutters).

MUC2 in Pseudomyxoma Peritonei

Through immunocytochemical studies, *in situ* hybridization and digital image analysis, O'Connell et al. [42,48] indicated that primary ovarian mucinous tumors essentially express MUC5AC whereas all solitary mucinous tumors of the appendix, as well as the different categories of PMP studied, express both MUC2 and MUC5AC. These findings not only supported earlier studies suggesting an appendiceal rather than ovarian origin for PMP [38-41], but more precisely implicated MUC2-expressing goblet cells as the putative cells of the origin in the pathogenesis of the disease. MUC2 is dramatically overexpressed in PMP through an epigenetic, rather than genetic, mechanism. Using pooled cases of PMP, O'Connell et al. [42], reported high levels of steady-state MUC2 mRNA with no corresponding gene rearrangement or amplification. On the other hand, they indicated that the constitutive level of MUC2 expression observed in normal goblet cells of the appendix is maintained by the proliferating tumor cells, irrespective of degree of their malignant tendency. On this basis, they concluded that PMP is a neoplastic disease of MUC2-expressing goblet cells in which tumor cells collectively, but not individually, overexpress MUC2 due to an increase in their number [42]. O'Connell et al. [42] also showed that PMP expression of MUC2 can be epigenetically regulated. They found that primary PMP cells upregulated MUC2 expression in response to 5-azacytidine, a DNA methylation inhibitor, and, more potently, after exposure to *Pseudomonas aeruginosa* lipopolysaccharides (LPS). These expression-enhancing effects were suppressed by genistein, a potent tyrosine kinase inhibitor. These studies alongside the ensuing investigations evaluating the expression of mucin subtypes in PMP (Table 2) have collectively implicated MUC2

as a key element in the pathogenesis of the disease with potential use as a molecular marker and a therapeutic target.

MUC2, MUC5AC, and MUC5B are the three gel-forming mucins reportedly expressed in PMP (Table 2). MUC2, however, is the PMP's specific and predominant mucin. With PMP and ovarian cancer both expressing MUC5AC, it is MUC2 which differentiates mucinous deposits of the former from mucinous implants of the latter. On an equimolar basis, MUC2 is more extensively glycosylated, hence more voluminous, than MUC5AC, thus responsible for the high degree of gelation in PMP. This gives rise to a significant difference between mucin:cell ratio of their mucinous secretions, that is 10:1 in PMP vs 1:1 in ovarian cancer [42]. In PMP, the accumulation of extracellular mucin is the real cause of the morbid, and potentially fatal, complications, irrespective of the site of origin, the mechanism of peritoneal spread, or the level of neoplastic transformation. The progressive accumulation of intra-abdominal mucin and its associated inflammatory/fibrotic reaction leads to intestinal obstruction, which is the major complication of the disease. Most of the tumor cells in the peritoneal cavity are surrounded by a mucin barrier, which help them move freely with the normal flow of the peritoneal fluid, "redistribute" around the peritoneal cavity and accumulate at specific abdominal and pelvic sites to create the distinctive feature of PMP. Additionally, the tumor cells are shielded by this barrier against immune recognition or chemotherapeutic effects [59].

MUC2: A Potential Therapeutic Target in PMP

Based on the clinicopathological features of PMP, the standard of care is centered on the maximal removal of tumor/mucin mass. This currently includes cytoreductive surgery This currently includes cytoreductive surgery followed by hyperthermic (or heated) intraoperative peritoneal chemotherapy (*HIPEC*) [60]. Despite aggressive therapies, PMP frequently recurs. This warrants novel therapeutic interventions, in particular those targeting mucin as a key player in the pathophysiology of PMP. Targeted reduction of MUC2 may provide a unique strategy for disease control and could potentially improve the efficacy of conventional therapies [59]. Since MAPK pathway has been implicated in MUC2 hypersecretion [61,62], MEK inhibitors (e.g., RDEA119, BAY 86–9766) may represent a novel strategy to decrease MUC2 production. Because of cross-talk between MAPK and other inflammation-associated signaling pathways, multi-targeted agents (e.g., Rapamycin, BAY 11–7085) may be more effective [63]. Cytokines have been implicated in goblet cell hyperplasia/metaplasia and mucin hypersecretion [64-66]. Glucocorticoids have been shown to directly inhibit MUC2 production via glucocorticoid response elements (GREs) in the promoter region and indirectly via transrepression of inflammation-associated transcription factors [67,68]. Similarly, COX-2 is overexpressed in a number of tumors including PMP [69]. Therefore, chronic anti-inflammatory drugs like dexamethasone and celebrex may control MUC2 secretion in PMP by suppressing the inflammatory environment that is conducive to mucin production [70]. The extent of MUC2 promoter methylation closely correlates with MUC2 expression in colorectal cancer cell lines, with mucinous cell lines exhibiting low-level methylation as compared to non-mucinous cell lines. This provides another potential target for the manipulation of MUC2 expression [71]. The Sp-family of transcription factors inhibits MUC2 promoter methylation, thereby augmenting MUC2 expression.The Sp1 binding site inhibitor mithramycin effectively blocks MUC2 expression in colorectal cancer [62,72].

Along with offering state-of-the-art services to patients with PMP [73-79], our team at St George Hospital is also extensively involved in different areas of cancer research, with PMP comprising a field of particular interest. We are currently conducting a comprehensive

Study	Year	Number of PMP cases	Percentage of cases exhibiting the expression of mucins	
			MUC2	**Other forms of mucins**
O'Connell et al. [48]	2002	25	96%	MUC5AC 92%
O'Connell et al. [42]	2002	100	98%	MUC5AC 95%
Mohamed et al. [49]	2004	33	97%	MUC1 57.5%
Kinkor et al. [50] *	2005	3	?	-
Nonaka et al. [51]	2006	42	100%	MUC5AC 100%
Mall et al. [52]	2007	1	100%	MUC5AC 100% MUC5B 100%
Ferreira et al. [53]	2008	7	100%	MUC1 28.6% MUC5AC 100% MUC6 28.6%
Semino-Mora et al. [54]¶	2008	16	N/A‡	N/A‡‡
Flatmark et al. [55]	2010	5	100%	MUC1 0% MUC5AC 40% MUC4 100%
Guo et al. [56]	2011	35	94.3%	MUC1 0%
Mall et al. [57]	2011	1	100%	MUC1 0% MUC4 100% MUC5AC 100% MUC5B 100% MUC6 0%
Chang et al. [58]¶	2012	4	64% †	MUC5AC 43% ††

* Full-text article, in Czech, not accessible. Results of IHC study not available.

¶ This study reports the expression of MUC2 and MUC5A as the volumetric density of apomucin (Vvi/10^4μm) in such compartments of DPAM and PMCA tissues as epithelium, lymphoid aggregates, stroma vessels and free mucin, respectively, as follows:

‡ MUC2: in DPAM: 264 ± 60, 47 ± 16, 31 ± 14 and 261 ± 51; in PMCA: 356 ± 90, 170 ± 26, 117 ± 25 and 1043 ± 282.

‡‡ MUC5AC: in DPAM: 90 ± 13, 345 ± 20, 65 ± 17, 37 ± 6; in PMCA: 56 ± 12, 246 ± 17, 50 ± 15 and 48 ± 9.

¶ In this study, among a total of 14 patients with mucinous adenocarcinoma, 4 cases have reportedly exhibited PMP syndrome. Results of the expression of MUC2 and MUC5AC, however, are reported in total, with no data individually available regarding the PMP cases.

†, †† Data shown is the percentage of MUC2/MUC5AC expression in all patients with mucinous adenocarcinoma, including PMP ones.

Table 2: A number of studies investigating the expression of mucin subtypes in pseudomyxoma peritonei.

PMP project, including preclinical and clinical studies, to develop new approaches and techniques to complement the conventional interventions. As the key factor in the pathogenesis of the disease and its morbid complications profoundly affecting the patients' survival and quality of life, mucin comprises a major part in our investigations. A number of ongoing studies are as follows: I. We are currently testing some novel mucolytic preparations with cytotoxic effects on mucin-producing tumor cells to be administered intraperitoneally for microscopic loco-regional cytoreduction purposes [80]. II. An animal model of PMP has already been established [81] and other models of PMP-like syndromes and peritoneal carcinomatosis are being developed for preclinical assessment of the mucolytic agents. III. An enzymatic formulation (bromelain combined with N-acetyl cysteine) has been also developed with promising preliminary results on mucin samples from PMP cases as well as on mucin-secreting in vitro models (unpublished data). Anticipated potential benefits of our novel approach include enhancement of surgical procedures in reducing tumor burden and mucin deposits, alleviation of morbidity, and potentiation of chemotherapy. These are currently being tested in preclinical and clinical settings.

Conclusion

PMP is a clinical syndrome with debilitating complications. Ectopic mucin-expressing goblet cells exfoliated from a primary mucinous tumor of the appendix are evidently putative cells of origin. Although PMP exhibits a low-grade neoplastic nature, it is progressive and recurrent. In PMP, tumor cells rarely invade and metastasize. However, they keep producing mucin regardless of the level of neoplastic transformation. Ectopic mucin is secreted into the peritoneal cavity where it is unable to drain away and thus accumulates. Due to the nature of tumor cells, multifocal collections develop within the peritoneal cavity. Recurring mucin deposits are responsible for morbid complications of the disease.

MUC2 is the major player in PMP. It forms voluminous, gelatinous collections with compressive effects on vital organs. MUC2 also protects tumor cells against immune response and chemotherapeutic-induced cytotoxicity. Progressive nature of the disease together with morbidity severely impact patient's survival and quality of life. Despite invasive cytoreductive surgery and peritonectomy, PMP relapses. Over the progression of the disease, suitable therapeutic options become more and more limited. This warrants novel therapeutic strategies to complement conventional approaches. Targeted therapies directed against upstream and downstream of different regulatory pathways of MUC2 expression and efficient mucolytic agents capable of dissolving mucin are among strategies of potential benefit which warrant further investigation.

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