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Review

Mucins and tumor resistance to chemotherapeutic drugs

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ABSTRACT

Epithelial cancer patients not considered eligible for surgical resection frequently benefit from chemotherapy. Chemotherapy is the treatment of cancer with one or combination of cytotoxic or cytostatic drugs. Recent advances in chemotherapy allowed a great number of cancer patients to receive treatment with significant results. Unfortunately, resistance to chemotherapeutic drug treatment is a major challenge for clinicians in the majority of epithelial cancers because it is responsible for the inefficiency of therapies.

Mucins belong to a heterogeneous group of large *O*-glycoproteins that can be either secreted or membrane-bound. Implications of mucins have been described in relation to cancer cell behavior and cell signaling pathways associated with epithelial tumorigenesis. Because of the frequent alteration of the pattern of mucin expression in cancers as well as their structural and functional characteristics, mucins are thought to also be involved in response to therapies. In this report, we review the roles of mucins in chemoresistance and the associated underlying molecular mechanisms (physical barrier, resistance to apoptosis, drug metabolism, cell stemness, epithelial–mesenchymal transition) and discuss the therapeutic tools/strategies and/or prognosis biomarkers for personalized chemotherapy response that could be proposed from these studies.

Contents

Abbreviations: PDAC, Pancreatic ductal adenocarcinoma; CRC, Colorectal cancer; EMT, Epithelial–mesenchymal transition; MUC1-CT, MUC1 cytoplasmic tail; N-t, Amino-terminal; C-t, Carboxy-terminal; PTS, Proline Threonine Serine

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1. Introduction

Mucins belong to a heterogeneous group of large *O*-glycoproteins composed of a long peptidic chain (called apomucin) on which are linked hundreds of oligosaccharidic chains. Initially, the mucin word designated glycoproteins secreted by specialized epithelial cells, the goblet cells, as part of the mucus gel. Mucins were biochemically characterized as massive molecules with high molecular weight able to form viscoelastic gels and responsible for the rheological properties of mucus [1]. The molecular era that led to genome sequencing allowed the classification of two sub-groups of mucins: (i) secreted mucins that mostly complied with this definition and (ii) membrane-bound or transmembrane mucins that did not fit in. Despite this dichotomy, mucins were all included in the MUC family with the approval of Human Genome Organization Gene Nomenclature Committee (HUGO/GNC) [2].

Secreted mucins are the major components of viscoelastic mucus gels and form a tridimensional network that protects the epithelia against various aggressions (inflammation, bacteria, virus, pollutants, pH, *etc.*). This subgroup mainly includes: MUC2, MUC5AC, MUC5B, MUC6 (clustered on the p15 arm of chromosome 11) and MUC19. MUC7 and MUC9 are smaller secreted mucins that do not oligomerize and are secreted by specialized cells as monomers [3–5]. Secreted mucins comprise amino- (N-t) and carboxyl-terminal (C-t) regions sharing structural domains with von Willebrand (vW) factor. The central part is enriched in Pro, Thr and Ser amino acid residues forming the variable PTS domain that is *O*-glycosylated [4]. The *O*-glycosylation process is crucial for mucin secretion, stability, processing, and functions during both development and pathophysiological conditions [6–8]. The adjacent CYS domains are highly hydrophobic and are believed to cause the aggregation of mucins [9]. By forming disulfide bonds, the main intestinal mucin MUC2 dimerizes *via* its C-terminal cysteine-knot (CK) domain and also trimerizes *via* N-t vWD domains building a complex molecular network [10,11]. On the contrary MUC5AC and MUC5B are linear disulfide-linked polymers that polydisperse and behave as random coils in solution [4].

The membrane-bound mucins are type I membrane-anchored proteins including MUC1, MUC3, MUC4, MUC12, MUC13, MUC15, MUC16, MUC17, MUC20, MUC21 and MUC22 [12–14]. Typically, membrane-bound mucins contain a long extracellular domain, a hydrophobic transmembrane domain, and a short cytoplasmic tail. Analysis of the peptidic sequences of mucins allowed description of their modular organization. The PTS domain, the only domain not conserved at the genomic level, is the common feature between mucins. Membrane-bound mucins share conserved domains such as epidermal growth factor-like (EGF) or Sea urchin sperm protein Enterokinase and Agrin (SEA) domains [13,15,16]. Based on their structure and localization at the cell surface they were shown to act in cell–cell, cell–extracellular matrix interactions and in cell signaling.

Mucins have a cell- and tissue-specific patterns of expression profoundly altered in epithelial cancers (loss of expression, overexpression, aberrant expression, neo-expression, glycosylation alterations) [17–21]. Because of their specific pattern of expression during the different steps of tumor progression toward adenocarcinoma, mucins stay under intense investigation as both potent new biomarkers and therapeutic targets in epithelial cancers.

Numerous reviews in the literature describe the roles of mucins in relation to cancer cell behavior and cell signaling pathways associated with tumorigenesis. Among them, membrane-bound mucins MUC1 and MUC4 have been extensively studied [14,22–25]. MUC1 and MUC4 govern both cellular differentiation and proliferation. They are also involved in metastasis and tumor proliferation. Secreted mucins MUC5B and MUC5AC and membrane-bound mucins MUC13 and MUC16 have also been associated with aggressive behavior of cancer cells [26–31]. On the contrary, Muc2 is involved in the suppression of colorectal cancer (CRC) since $Muc2^{KO}$ mice develop adenoma progressing with age to invasive adenocarcinoma [32].

The dramatic outcome of epithelial cancers of the gastrointestinal tract is often related to a lack of both efficient therapeutic tools and early diagnostic markers. Patients not considered eligible for surgical resection frequently benefit from chemotherapy. However, chemoresistance is a common feature of epithelial cancers. Lately, mucins have been proposed as actors of this phenomenon. In this review, we discuss their role in chemoresistance and the associated cellular mechanisms to propose them as therapeutic tools and/or prognosis biomarkers of chemotherapy response.

2. Mucins and chemoresistance *in vitro*

In our laboratory and others, initial *in vitro* studies showing the relationship between mucins and chemoresistance came from colorectal carcinoma cells (HT29) stably resistant to 5-fluorouracil (5-FU) or methotrexate [33–35]. These cells were characterized by the overexpression of secreted mucins when they became resistant cells. This observation pointed out to the potential of mucins as actors of chemoresistance (Table 1).

In breast cancer cells, the overexpression of MUC1 is involved in cell sensitivity to Herceptin® *via* the increase of the cleavage of this mucin. These cells are also resistant to paclitaxel (Taxol®), doxorubicin and cyclophosphamide, suggesting a broader involvement of membrane-bound mucins [36]. Similarly, silencing the *MUC1* or *MUC4* gene can reverse resistance to trastuzumab in HER2-positive gastric cancers [37,38].

Xenograft tumors of estrogen receptor positive (ER)/HER2-overexpressing breast cancer cells, that are developing resistance to lapatinib and trastuzumab, harbor an increase in mucin-filled vacuoles and upregulation of several mucins including MUC4 [39] suggesting a role of MUC4 in acquired resistance to chemotherapy. MUC4 influence on chemosensitivity has mainly been studied in pancreatic cancer cells using gain or loss of function strategies. Several reports showed that MUC4 protects pancreatic cancer cells from gemcitabine-induced cytotoxicity [40–43]. Similar observation was made regarding another cytidine analog, the cytarabine/aracytin ARA-C [42] or 5-fluoro-uracile (unpublished data). Overexpression of rat ortholog MUC4/SMC in melanoma cells also reverts antiproliferative effect of taxol, doxorubicin, vinblastine, rhodamine-123 or 2-deoxyglucose and cell death induced by doxorubicin [44]. Finally MUC4 expression was shown to reduce the mitochondrial damage in pancreatic cancer cells induced by

Table 1
Mucins and drug chemoresistance in epithelial cancer cells.

Mucin	Drug	Tumor type	Refs
Membrane-bound mucins			
MUC1	5-FU/methotrexate	CRC	[34,35]
	5-FU	PDAC	[58,60]
	Cisplatin	Ovarian	[52]
	Cisplatin	CRC	[67]
	Taxane/platinum compound	Ovarian	[53]
	Trastuzumab/paclitaxel/doxorubicin/cyclophosphamide	Breast cancer	[36]
	Gemcitabine/etoposide	PDAC	[90]
MUC3	Methotrexate	CRC	[34]
MUC4	5-FU	CRC	[34]
	Lapatinib/trastuzumab	Breast cancer	[39]
	Trastuzumab	Melanoma/breast cancer	[65]
	Cytarabine/aracytin	PDAC	[42]
	Paclitaxel/doxorubicin/vinblastine/rhodamine-123/2-deoxyglucose	Melanoma	[44]
	Bortezomib	PDAC	[43]
	Gemcitabine	PDAC	[40–42]
Secreted mucins			
MUC5AC	5-FU/methotrexate	CRC	[34,35]
MUC5B	5-FU/methotrexate	CRC	[34,35]
MUC2	5-FU	CRC	[34]

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