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Targeting MUC16 in Cancer Therapy

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Abstract

Over the recent decades, there has been a number of studies investigating the role of mucins in the pathogenesis of various cancers such as breast, lung, ovarian, gastrointestinal and pancreatic malignancies. Since then, it has been discovered that mucins play a critical role in tumorigenesis as they can mediate cell proliferation, metastasis and resistance to chemotherapy. Thus, mucins have been explored as a potential therapeutic target as well as a biomarker, as cancer cells often have an aberrant expression of mucins. MUC16 is a glycoprotein coded by one of the 21 mucin genes. CA125, the extracellular domain of MUC16, is a well-established biomarker for ovarian cancer, however there is no in depth literature review on MUC16 as a target for anti-cancer therapy. Thus, this review summarises the existing literature on MUC16, the current therapies targeting on MUC16 and highlights future avenues for targeting mucin-producing cancers.

Keywords: MUC16; Mucins; Ovarian cancer; Pancreatic cancer; Metastasis; Immunotherapy; Mucolytic agents

Abbreviations MUC: Mucin; EMT: Epithelial Mesenchymal Transition; JAK: Janus Kinase.

Introduction

MUC16 is a type of Type 1 transmembrane mucin with a molecular weight of 3-5 million Da [1], making it the largest glycoprotein out of the mucin family. It is a well-established biomarker used to monitor the progression and recurrence of ovarian cancer. Furthermore, it is overexpressed in a range of human malignancies including ovarian, pancreatic, breast, cholangiocarcinoma, cervical, gastric and non-small cell lung cancer [1-6]. Mucins are a family of high molecular weight glycoproteins composed of oligosaccharides attached to a peptide core [7]. There are three main components to MUC16 including an extracellular N-terminal domain, tandem repeat domain and carboxyl terminal section as seen in Figure 1. Several hundred oligosaccharides are attached to the N-terminal domain through O-linked glycosylation and N-linked glycosylation whilst the tandem repeat region (TRR) has approximately 60 repeats of a 156 amino acid sequence, with disulphide bonds that confers structural stability. Attached to the TRR is a smaller C-terminal domain that also contains a cytoplasmic tail involved in intracellular cell events (Figure 1) [1,3,8].

Importance of MUC16 in Cancer

MUC16 is normally present in the respiratory, reproductive and corneal epithelium. As a large glycoprotein, it is able to form a chemical barrier to protect the epithelium against hostile environmental conditions and pathogens [1,9]. However, cancer cells have an aberrant expression of mucins, which confers a number of oncogenic properties such as increased cell proliferation, evasion of the immune system and metastasis [1,3,10].

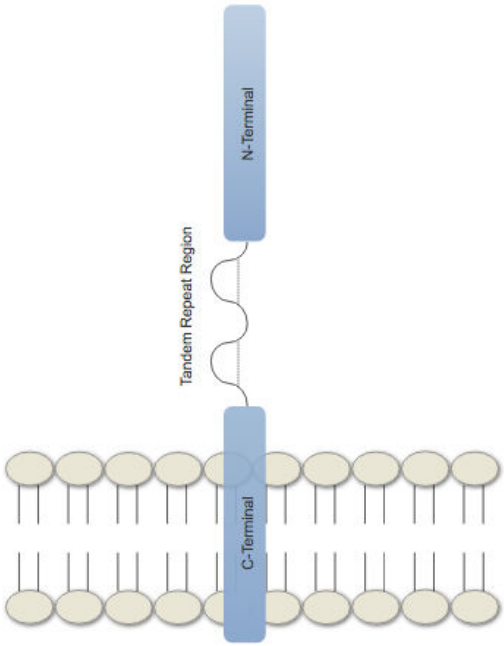

Figure 1: Structure of MUC16.

Ovarian cancer

More than 80% of epithelial ovarian cancers overexpress MUC16, also known as CA125 [11,12]. CA125 is part of the extracellular portion of MUC16 that can be shed into the circulatory system [10]. Therefore, serum levels of CA125 are used to monitor disease status and recurrence after surgery or radiotherapy [13,14]. Functionally,

MUC16 is an important molecule in metastasis through modulating E-cadherin, N-cadherin and vimentin expression [15-17]. MUC16 also binds to mesothelin, a protein involved in peritoneal metastases of ovarian cancers. Other properties include inhibition of apoptosis, contributing to chemotherapy resistance [8,11,18] and activation of STAT3 through JAK2, which increases cell proliferation [3,13]. Additionally, MUC16 is implicated in reducing the immune system response by binding to inhibitory receptors on natural killer (NK) cells [1,19] and decreasing expression of CD16, a cytokine that stimulates NK cells [20,21].

Pancreatic cancer

There is a progressive increase in the expression of MUC16 from the precursor pancreatic intraepithelial neoplasia to adenocarcinoma, further suggesting its significance in tumorigenesis [22,23]. Furthermore, MUC16 has been reported to correlate with higher metastatic burden, and serum CA125 levels at baseline was a predictive factor for metastasis after resection [9,24,25]. A number of mechanistic studies have shown that MUC16 binds to mesothelin, E and P selectin and upregulates the FAK mediated Akt pathways, which confers metastatic properties [10,26-28]. Other oncogenic properties of MUC16 include reprogramming metabolism [29] and increasing cell proliferation through JAK2 [30]. A number of other studies have also looked into the importance of MUC16 in mediating resistance to therapy. Mucins in general have been implicated in resistance through a number of mechanisms including forming a physical barrier around the tumour cell [31]. Specifically, MUC16 is involved in inhibiting apoptosis and blunting the cellular response to genotoxic drugs [32]. As it plays an important role in the oncogenesis, MUC16 has garnered attention as a biomarker to monitor disease and predicting response to therapy [2,7,33].

Breast cancer

MUC16 is overexpressed in breast carcinomas [34]. Functionally, the MUC16 glycoprotein interacts with JAK2, resulting in the phosphorylation of STAT3, inducing cell proliferation. MUC16 also down regulates the tumour necrosis factor-related apoptosis-inducing ligand apoptotic pathway (TRAIL) [35]. Hence, MUC16 knockdown in breast cancer cells resulted in increased apoptotic rates, suggesting again that it plays an important role in cancer cell survival [36].

Lung cancer

MUC16 is associated with invasive lung cancer and predicts a poorer clinical prognosis in those with metastatic lung cancer through mediating chemoresistance and increasing the aggressive of the cancer [37]. Furthermore, it is also involved in mediating resistance to platinum based genotoxic drugs through increased expression of TSPYL5 (testis-specific Y-like protein). TSPL5 can subsequently bind to ubiquitin specific protease to inactivate p53, a tumour suppressor protein [3].

Bladder cancer

Similarly, MUC16 stimulates angiogenesis and mediates metastasis in advanced bladder cancer and may have clinical utility as a biomarker. However, further work is needed to elucidate the functional significance of MUC16 in urological malignancies [38].

Oral squamous cell carcinoma

In a study involving 97 patients, CA125 levels were measured with ELISA between oral squamous cell carcinoma, non-neoplastic disease of the oral cavity and controls. CA125 levels were higher in the saliva of those with oral squamous cell carcinoma compared to those with non-neoplastic disease or healthy controls. However levels didn't correlate with grade or prognosis [39].

MUC16 as an Anti-Cancer Target

The most common therapeutic approach has been using antibodies against the tandem repeat region of MUC16, specifically CA125. However, other emerging therapies and potential avenues of treatment also exist.

Anti-MUC16 antibodies

There have been a number of antibodies developed against CA125, an epitope of MUC16 contained in the tandem repeat region, for the treatment of ovarian cancer as a potential front line therapy, and a maintenance drug to prevent recurrence disease [8]. Mab-B43.13, also called oregovomab, is a monoclonal antibody that binds to CA125 forming antigen-antibody complexes to stimulate an immune response [40,41]. Although patients had a measurable increase in both T and B cells [42,43], clinically it was met with limited success [44].

Abagovomab, is an anti-idiotypic antibody targeting CA125 in ovarian cancer. It is designed chemically similar to the tumour antigen, thus eliciting an immune response against the cancer cells [45]. Although it showed potential in Phase I and II trials, ultimately the therapy failed to show significant benefit over the placebo [46-48]. Interestingly, patients with cytotoxic T-cells (CTLs) against MUC16 had a better clinical prognosis regardless of whether they received therapy, suggesting the importance of MUC16 in ovarian cancer [49]. Other than monoclonal antibodies, studies have also investigated the use of vaccinations such as the ACA125 vaccine, which showed a 3-month improvement in progression free survival in patients with advanced ovarian cancer [50,51]. Similarly, another preclinical study investigating a MUC16 vaccine showed that patients generated an IgG response, however the clinical utility is yet to be determined [52]. Overall, immunotherapy has shown limited benefit. This may be due to the fact that the extracellular domain of MUC16 undergoes cleavage, which reduces the binding of these monoclonal antibodies to the tumour cells. Furthermore, due to the shedding of MUC16, it is also likely that the drug binds to circulating MUC16 in the serum, hence only a small fraction ever reaches the tumour cells [8]. Therefore, to improve current immunotherapy for MUC16, it would be necessary to generate antibodies against the carboxyl terminal domain that does not undergo cleavage. Currently, Dharma et al. has developed an antibody binding to the carboxyl terminal domain of MUC16, which is retained by the tumour cells after cleavage. However, this has only been performed *in vitro* [53].

Adoptive immunotherapy

CAR (chimeric antigen receptor) T cells are genetically modified T cells that express a receptor for a specific tumour antigen. They are able to bind to the tumour cell with higher affinity, magnifying the cytotoxic T cell killing effect. Recently, a CAR T cell expressing the MUC16 epitope has been designed for a Phase I clinical trial. In order to enhance the efficacy of the treatment, the T cell has also been

modified to increase the expression of IL-12, a cytokine with anti-cancer properties [54]. Another similar study had looked at CAR T cells expressing MUC16, which had cytotoxic effects *in vitro* and completely eliminated the tumour in murine models [55]. The clinical benefit of these therapies over existing regimens, however, needs to be evaluated.

Targeting interactions between MUC16 and downstream targets

MUC16 interacts with a number of oncogenic proteins such as mesothelin, an important molecule that regulates cell adhesion, strongly implicated in peritoneal metastases of ovarian cancer [56]. HN125 is an immunoadhesin that has a high affinity for MUC16. It was created by combining mesothelin with the constant domain of human immunoglobulin. By binding to the glycoprotein, it can antagonize the interaction between MUC16 and mesothelin, therefore inhibiting the spread of ovarian cancer. Furthermore, it was also able to generate an antibody dependent cytotoxic response against MUC16 expressing ovarian cancer cells. Immunadhesins therefore can be an alternative method of immunotherapy in cases where monoclonal antibodies have failed [57]. A similar antibody MORAb-990 that antagonises the binding of MUC16 to mesothelin has also been explored in a Phase I trial and showed an additional benefit of chemosensitization [58].

Antidrug conjugates

As cancer cells overexpress MUC16, by binding the drug to an anti-MUC16 monoclonal antibody this specifically targets tumour cells. Utilising this method in MUC16 positive cancer has reportedly reduced systemic side effects and improves potency of the drug [8]. Currently it has been tested in a Phase I clinical trial where the drug monomethyl auristatin E was bound to anti-MUC16 antibodies. One patient had a complete regression of their tumour whilst five has a reduction [1]. In another Phase 1 multicenter study they conjugated the same drug to another MUC16 antibody DMUC5754A and administered it to 66 platinum-resistant ovarian cancer patients and 11 unresectable pancreatic cancer patients. Six patients had a positive response whilst for two of the patients the drug was able to stop the progression. CA19-9 serum levels were measured to monitor response rate [59]. Another *in vitro* study has investigated Meso-TR3, a recombinant protein combining mesothelin and TR3, that binds to MUC16. By combining the drug TRAIL (TNF-related apoptosis inducing ligand) with Meso-TR3, a higher concentration of the drug reached the ovarian cancer cells resulting in an upregulation of apoptosis for both *in vitro* and animal studies [60].

Mucolytic agents

Considering the difficulty of targeting MUC16, an alternative therapeutic approach would be to utilise mucolytic agents that deplete mucins in general. One such combination is the use of bromelain and N-acetylcysteine. Bromelain, an extract from pineapple stem, is a mixture of proteolytic enzymes able to cleave glycosidic bonds in mucins [61] and is traditionally used as a complementary medicine for its anti-inflammatory and anti-thrombotic effects [62]. N-acetylcysteine is a derivative of a natural amino acid, used as a mucolytic agent in conditions such as cystic fibrosis and also as an antioxidant for acetaminophen poisoning [63,64] and is able to cleave disulphide bonds that stabilize the mucinous structure [65]. Recently, the combination has garnered attention as an anti-cancer agent, particularly in regards to its mucolytic properties.

The utility of bromelain and N-acetylcysteine has been investigated in a number of mucin producing cancers such as malignant pleural mesothelioma [61,66], gastrointestinal cancers [65,67-69]. These *in vitro* studies have shown that bromelain and N-acetylcysteine synergistically reduces mucins, thus depleting the cells of an essential protective framework resulting in increased cell death as well as increased chemosensitivity [61,65-69].

Conclusion

Although it is used widely as a biomarker for ovarian cancer, it is clear that MUC16 plays an important role in the pathogenesis of a number of human malignancies such as ovarian, breast, colorectal and pancreatic cancer. However, we are yet to completely understand the mechanism of MUC16 in facilitating tumour growth and invasion and currently we do have any effective therapies against MUC16. One of the major barriers to achieving this therapeutic goal is that the structure and function of MUC16 is not well characterised. Additionally, the majority of the methods for therapy and clinical trials have focused primarily around ovarian cancer. This review highlights the unexplored capacity of MUC16 as a potential therapeutic target in namely pancreatic and breast cancers, and the importance of examining these other mucin-producing tumours.

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