Published in final edited form as:

Lancet Oncol. 2008 November ; 9(11): 1076–1085. doi:10.1016/S1470-2045(08)70277-8.

Clinical potential of mucins in diagnosis, prognosis, and therapy of ovarian cancer

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Abstract

Knowledge of mucins and their multiple roles in various normal and pathological processes has improved greatly in the past two decades. Mucins belong to a family of glycoproteins characterised by densely *O*-glycosylated repetitive domains and expressed by various surface epithelial cells. Altered expression of mucins is present in various diseases, including cancer. Ovarian cancer is the sixth most common cancer worldwide and the seventh leading cause of cancer-related deaths in women. The most common ovarian cancer is epithelial ovarian carcinoma, which is characterised by few early symptoms, widespread peritoneal dissemination, and ascites at advanced stages that result in poor prognosis. After diagnosis, 5 year survival is only 35–45%. Therefore, improved strategies for early diagnosis and treatment are needed. Because of the surface epithelial origin of epithelial ovarian cancer, mucins are obvious biomolecules for investigation as markers for early diagnosis and as therapeutic targets. We discuss the potential role and clinical usefulness of mucins in early diagnosis, prognosis, and treatment of ovarian cancer.

Introduction

Ovarian cancer is the sixth most common cancer worldwide and the seventh leading cause of cancer-related deaths in women.¹ One in 57 women in developed countries will develop ovarian cancer at some point in her lifetime. Incidence of ovarian cancer is highest in white and Hawaiian women, and lowest in Native American women.² According to epidemiological studies, family history is the strongest risk factor for the development of ovarian cancer, which further depends on the number of affected first and second-degree relatives.³ Among the genetic risk factors associated with hereditary ovarian cancers, mutations in *BRCA1* and *BRCA2* are thought to be particularly important.⁴ Age is another

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Conflicts of interest

The authors declared no conflicts of interest.

common risk factor for ovarian cancer. The incidence of ovarian cancer is increased after menopause, and advanced age (early 60s) at first diagnosis contributes to the high mortality associated with the disease. The ovaries of postmenopausal women typically become folded, resulting in the formation of deep clefts and small inclusion cysts lined with ovarian surface epithelial cells.^{3,5} These changes provide an environment for the development of ovarian cancer.⁶ Nulliparity, use of fertility drugs, and endocrine disorders are other risk factors for the disease.⁷ The risk of ovarian cancer also increases with the number of ovulatory events. Repetitive wounding and inflammation of the ovarian surface epithelium associated with ovulation might contribute to increased cell proliferation and mutation rates, which ultimately result in tumour formation.^{6,8} By contrast, multiparity, use of oral contraceptives, pregnancy, and lactation are associated with a lower risk of ovarian cancer because of the decreased number of ovulation cycles.^{3,9}

Most (90%) ovarian cancers are epithelial in origin and, hence, are referred as epithelial ovarian cancers. The remaining ovarian tumours are gonadal-stromal (6%), germ cell (3%), and metastatic (1%) tumours.¹⁰ The ovarian surface epithelium, which is the outermost cell layer of the normal ovary (figure 1), has no unique features or known major functions. Therefore, early cellular and molecular changes and minor anomalies remain undetected in epithelial ovarian cancers.¹¹ Nonetheless, aberrant fimbrial epithelium with hyperplasia and a p53 signature is a plausible precursor lesion for many advanced serous ovarian cancers.¹² Because of the anatomic location of the ovaries and the lack of early symptoms, clinical differentiation between benign, borderline, and malignant tumours is difficult. On the basis of epithelial characteristics, epithelial ovarian cancer is classified into five histological phenotypes: serous tumours (fallopian-tube-like epithelium), endometrioid proliferative (endometrium-like epithelium), mucinous tumours (endocervix or colonic epithelium), clear cell carcinoma (epithelium of the gestational endometrium), and transitional or Brenner tumours (epithelium of the urinogenital tract). Additionally, on the basis of disease advancement, ovarian tumours are subdivided into four progression stages (I–IV) according to the extent of metastasis.^{3,10} Because of the lack of adequate screening tools, epithelial ovarian cancer is diagnosed, in most cases, at stages III or IV, when it has already metastasised to the peritoneum or distant sites.

Mucins are high-molecular-weight glycoproteins widely expressed by epithelial cells of the gastrointestinal, respiratory, and urinogenital tracts that have multiple implications in cancer development.^{13–15} Because most ovarian cancers are of epithelial origin, mucins are attractive diagnostic and therapeutic targets. In fact, CA125, which is used in the diagnosis of epithelial ovarian cancer, is the mucin MUC16.¹⁵ Research suggests clinical importance of mucins in various cancers. We review the current knowledge on mucins in epithelial ovarian cancer and discuss their potential role and clinical usefulness in the diagnosis, prognosis, and treatment of this disease.

Diagnosis and therapy

Most patients with early-stage epithelial ovarian cancer are asymptomatic or present vague symptoms, including abdominal fullness, dyspepsia, bloating, pelvic pain, and early satiety.^{7,16,17} Additionally, ascites, pleural effusions, and an umbilical mass known as a

Sister Mary Joseph nodule, may be evident. For non-invasive diagnosis, transvaginal sonography of the pelvis is the preferred screening method. Serum concentrations of MUC16 are high in more than 80% of patients with advanced epithelial ovarian cancer, and this measurement is routinely used in diagnosis.¹⁷ However, transvaginal sonography and measurement of MUC16 both have limited specificity. Moreover, the concentration of MUC16 is raised in only a few patients with early disease. The limitations of current diagnostic methods have prompted researchers to investigate new markers of early disease to screen patients efficiently and monitor disease progression.

An exploratory or complete surgical intervention (laparotomy) is part of primary therapy, which facilitates precise staging and histopathological classification of the disease and tumour debulking.^{17,18} After surgery, systemic chemotherapy is commonly used to eradicate residual disease. Postoperative chemotherapy typically includes taxane and platinum-based adjuvant treatments, which act by different mechanisms. Taxanes, such as, paclitaxel and docetaxel, bind to tubulin polymers leading to their stabilisation; whereas the platinum analogues (cisplatin and carboplatin) form intrastrand cross-links with DNA and are the most active agents for the treatment of this disease.^{17,19} Combination chemotherapy with both taxane and platinum analogues has also been investigated, and data from randomised trials have led to use of combined carboplatin and paclitaxel as standard first-line-treatment.^{20,21} Some evidence supports the use of radiation-based therapy, particularly for chemo-resistant ovarian cancer;^{22,23} however, radiotherapy remains controversial for advanced epithelial ovarian cancer because of toxic effects.²⁴

Mucins: multifunctional glycoproteins

Mucins are high molecular weight biomolecules produced by the secretory epithelial cells lining ducts and lumens within the human body. The key role of mucins is to keep epithelial surfaces hydrated, which is needed for the lubrication and proper functioning of ducts and passageways. In addition, mucins are implicated in the protection of the epithelial cells from infections and injuries.^{13,25} Mucins are also involved in renewal and differentiation of the epithelium, modulation of cell adhesion and signalling, and immunosuppression.^{25,26} All of these properties and functions of mucins have raised interest for further investigation into the biochemical properties and biological implications of mucins.^{13,25} The hallmark of all mucins is the presence of large *O*-glycosylated tandem-repeat domains rich in serine, threonine, and proline that vary in length because of genetic polymorphism.²⁵ The molecular weight of mucins primarily depends on size and degree of the *O*-linked glycosylation of the tandem-repeat domains. 18 human mucin genes have been identified: *MUC1*, *MUC2*, *MUC3A*, *MUC3B*, *MUC4*, *MUC5AC*, *MUC5B*, *MUC6*, *MUC7*, *MUC8*, *OVGP1* (*MUC9*), *MUC11/12*, *MUC13*, *MUC15*, *MUC16*, *MUC17*, *MUC19*, and *MUC20*.²⁵ These mucins are grouped into two classes, secreted and membrane-bound, on the basis of their structural characteristics and physiological fate.

The membrane-associated mucins are encoded by 10 genes (*MUC1*, *MUC3A*, *MUC3B*, *MUC4*, *MUC11/12*, *MUC13*, *MUC15*, *MUC16*, *MUC17*, and *MUC20*). These mucins have multiple biological functions. Of particular importance is their role in signal transduction and modulation of cancer-cell behaviour leading to the potentiation of tumorigenicity and

metastasis.^{14,25} Many membrane-associated mucins (MUC3A, MUC3B, MUC4, MUC12, MUC13, and MUC17) have two or three structural motifs in their juxtamembrane region with sequence homology to epidermal growth factor (EGF), referred to as EGF-like domains.²⁵ The precise function of these domains is unknown; however, they might allow membrane mucins to interact with the EGF-receptor family members and regulate EGF-receptor-mediated cell signalling.²⁵ In addition to their structural motifs, the functions of these mucins depend on the degree and nature of *O*-glycosylation of the tandem-repeat domains. The oligosaccharide structures on mucins are involved in specific ligand–receptor interactions.^{13,25} The large extracellular domain of mucins might prevent the interaction of cell-adhesion molecules to their respective ligands by steric hindrance and hence, the overexpression of membrane-bound mucins can affect the cell–cell interaction and cell adhesion to the extracellular matrix.^{14,25}

The secreted mucins form most of the mucus and are expressed by specialised epithelial cells with a restricted expression pattern within the human body. Secreted mucins have been divided into two subclasses: gel-forming (MUC2, MUC5 (MUC5AC), MUC5B, MUC6, and MUC19) and non-gel-forming (MUC7).²⁵ Oviduct specific glycoprotein (OVGP1 [MUC9]) also belongs to this class, but is not well characterised. The gel-forming ability of these mucins is due to the oligomerisation of the core protein mediated by the D domain (named D domain because of its homology with dimerisation domain of von Willebrand factor).²⁵ The volume and composition of the gel matrix is determined by the mucin types, nature of their post-translational modifications, degree of the intramolecular and intermolecular cross-linking, and the types of molecules that are captured in the gel.^{13,25,27} The thick gel-matrix forms a barrier to protect the epithelia of airways, ducts, and digestive tract from microorganism, toxins, acids, proteases, and other digestive enzymes. Additionally, the gel-forming mucins capture and hold biologically active molecules, such as trefoil factors.^{13,25} Coordinated expression and co-localisation of certain specific mucins and trefoil factors have been reported in the normal and ulcerated gastrointestinal tract.²⁸ The specific activities associated with trefoil factors include the promotion of cell growth and motility, cell differentiation, and antiapoptotic effects. The coordinated aberrant expression of trefoil factors and mucins in premalignant and cancer cells raises the possibility that these molecules might contribute to the malignant phenotype of tumour cells.^{28,29}

Mucins in ovarian cancer development

The ovarian surface epithelium has a mixed epithelio-mesenchymal phenotype and is the only region in the ovaries that expresses mucins.^{3,5} Normal ovaries do not consist of any glandular tissue or goblet cells; therefore, no secreted mucins are expected to be synthesised by the parenchyma of the ovary. Among the membrane-anchored mucins expressed by the ovarian surface epithelium in normal conditions, MUC1 is the best studied.^{5,16} Cultured non-malignant ovarian epithelial cell lines also express MUC1 and MUC5AC.³⁰ Epithelial ovarian cancers are among the most variable tumours of any organ because of the phenotypic resemblance of ovarian tumour cells with the epithelia of different organs.³ Although the mechanisms are unclear, many epithelial ovarian cancers express more mucins than normal ovarian surface epithelium and benign ovarian tumours. MUC1, MUC2, MUC3,

MUC4, MUC5AC, and MUC16 are overexpressed in epithelial ovarian cancer (table 1).^{3,17,30–38}

The role of different mucins has not been extensively studied in epithelial ovarian cancer development. Ovarian cancer has a unique pattern of progression. According to an earlier concept, no tumour is found on the surface of the ovary;³ however, as the tumour grows, the intact ovarian outer surface is disrupted and the cancer extends to the pelvic region. At this stage, the spreading of the tumour cells can occur by direct contact and invasion into the adjacent tissues, such as the uterus, fallopian tubes, bladder, sigmoid colon, or rectum. The exfoliated tumour cells float in the peritoneal fluid and adhere to the mesothelial cells that line the inner wall of the peritoneum and the outer surface of different pelvic and abdominal organs. Half of the advanced serous cancers might originate from the fimbria of the fallopian tube, and, therefore, surface involvement might occur at an early stage in many advanced stage serous cancer.¹² Haematogeneous metastasis of ovarian cancer cells is a rare phenomenon, and can lead to involvement of organs, including the brain. The aberrant changes in mucin expression (mucin switching) during the transformation of normal ovarian surface epithelium to and cancer might be important in disease progression (figure 1). Aberrant mucin expression can change adhesive and antiadhesive properties of tumour cells, thereby promoting the dissemination of tumour cells during metastasis. A recent study has suggested a possible role of MUC1 in promoting the survival of the disseminated ovarian cancer cells under anchorage-independent condition by inhibiting anoikis in vitro.³⁹ Recent studies from our laboratory have also shown that MUC4 interacts with receptor tyrosine-protein kinase ERBB2 in pancreatic cancer cells and modulate its stability and downstream signalling.⁴⁰ Similarly, MUC1 interacts with EGF receptor 1 (EGFR ERBB1) in human breast epithelial cells and regulate its expression.⁴¹ The interaction of MUC1 with the EGFR results in phosphorylation of tyrosine residues on the cytoplasmic tail of both MUC1 and EGFR. The cytoplasmic tail of MUC1 induces several cell-signalling pathways that promote cell growth in various cancer cells.²⁵ MUC4 is highly expressed in the ovarian cancer cells in peritoneal effusions from 99% of the cases. Because MUC4 seems to have a role in the metastasis of pancreatic cancer,²⁶ investigation of the role of MUC4 in the peritoneal dissemination of ovarian cancer cells would be interesting. MUC16, another mucin aberrantly overexpressed in ovarian cancers, interacts with mesothelin, and this interaction might play a part in metastasis of ovarian cancer.^{42,43} Mesothelin is expressed by both the ovarian cancer and mesothelial cells, which are present on the surface of peritoneum and other abdominal organs. Therefore, the interaction of MUC16 and mesothelin might be important in both homotypic (tumour cell–tumour cell) and heterotypic (tumour cell–mesothelial cell) interactions of tumour cells. Homotypic interactions might increase multicellular spheroid formation in the peritoneal fluid and thus raise tumour load at the site of secondary metastasis, whereas the heterotypic interactions might improve adhesion of the ovarian cancer cells to peritoneal and other abdominal surfaces. MUC16 might also help tumour cells escape immune surveillance.^{44–46} MUC16 inhibits the cytolytic activity of the natural killer cells by downregulating the expression cell-activating receptor CD16. In the peritoneal cavity of patients with ovarian cancer, secreted MUC16 specifically interacts with CD16+ CD5(dim) natural killer cells, which are efficient mediators of cytotoxic responses. This interaction leads to change in phenotype of CD16+ CD5dim type natural killer cells

into CD16– CD5(bright) type, which have low cytolytic potential.^{44,46} MUC16 protects ovarian cancer cells from complement attack by trapping and shedding effectors of complement cascade.⁴⁵

Mucins as potential markers for diagnosis and prognosis

Differential expression of mucins in cancer makes them attractive targets for diagnosis and disease management. Several studies have investigated the potential use of secreted and membrane-bound mucins in the early diagnosis of cancer, disease classification, and prediction of clinical outcomes.^{17,26,47} Proteolytic cleavage or alternative splicing of transmembrane mucins result in secretion into the circulation. These secreted forms can be detected in patients' serum and might serve as potential tumour markers or markers for other disease. In fact, tumour antigens, such as CA19-9, 50, and 242 are present on mucin glycoproteins and are used clinically as serum markers of various malignant diseases.¹³

MUC16 is a tumour antigen and the established serum marker for the diagnosis of ovarian cancer.⁴⁸ Serum concentrations of MUC16 are raised in 80–90% of advanced-stage ovarian cancers, and this measurement has been used for the diagnosis of ovarian cancer.⁴⁹ Furthermore, the combined use of antibodies recognising distinct epitopes of MUC16 (such as OC125 and M11) has resulted in the improved specificity of this marker.⁵⁰ MUC16 is also useful in follow-up after treatment of ovarian cancer. Serum concentrations increase with disease progression, but decline after therapeutic intervention.⁵¹ Despite enormous importance in ovarian cancer diagnosis and disease management, the clinical usefulness of diagnosis based on MUC16 is compromised by lack of specificity and high rates of false-positive diagnoses. High concentrations of the marker are detected in other (pancreatic, breast, bladder, liver, and lung) cancers, benign diseases (diverticulitis, uterine fibroids, endometriosis, benign ovarian cyst, tubo-ovarian abscess, hyperstimulation syndrome, and ectopic pregnancy), and physiological conditions (pregnancy, menstruation).⁵¹ Therefore, newer approaches are needed to overcome the lack of specificity and sensitivity for early detection. Clinical trials of combinations of MUC16 measurement and ultrasound techniques, such as transabdominal or transvaginal sonography, or other biomarkers have been assessed for early detection of ovarian tumours and disease monitoring with promising results.⁵² To improve the sensitivity for detection, the expression of other mucins should also be examined in ovarian cancer. MUC4 is a good marker for early diagnosis of epithelial ovarian cancer and in combination with MUC16 can provide better sensitivity, even for advanced-stage cancers.¹⁷ This finding is consistent with a previous study reporting overexpression of MUC4 in most early stage ovarian tumours.³⁰ Furthermore, Davidson and colleagues⁵³ reported high expression of MUC4 in the ovarian carcinoma cells present in peritoneal effusions and showed the usefulness of this molecule as a biomarker for differentiation of ovarian cancer from benign and malignant mesothelial cells.⁵³ Thus, measurement of other mucins complementing MUC16, not only might allow early detection, but also might offer combined screening along with MUC16 to improve diagnostic sensitivity and accuracy of the assays. A combined panel of four biomarkers, three of which are mucins—MUC16 (CA125), MUC1 (CA15-3), and tumour associated glycoprotein 72 (CA72-4)—improved detection of stage I ovarian cancer.⁵⁴

Although certain tumours (mucinous and borderline carcinomas) have low concentrations of MUC16, the overall prognosis for people who test positive for this antigen is poor. Higher titres of MUC2, MUC3, and MUC4 mRNA were detected with northern-blot analysis in early stage ovarian tumour samples than were found in samples from late-stage. Additionally, expression of MUC2 and MUC4 mRNA was associated with better prognosis.³⁰ We recently reported overexpression of MUC1, MUC4, and MUC16 in several early and late-stage ovarian tumours by immunohistochemical analyses.¹⁷ We did not find an association of MUC4 concentrations with better prognosis, as previously reported.³⁰ In fact, a trend toward poor survival was observed in patients with ovarian cancer expressing MUC4. Importantly, we found a clear correlation of MUC16 with poor prognosis. Furthermore, another study suggested that the presence of MUC1 antibodies and factors that induce MUC1 immunity are inversely correlated with ovarian cancer risk.⁵⁵

Mucins as targets for radioimaging, radioimmunotherapy, and targeted delivery of cytotoxins

In addition to their use as diagnostic markers, the overexpression of cell-surface mucins also makes them useful targets for live-imaging and treatment of cancer. Radiolabelled monoclonal antibodies directed against cell-surface mucin antigens combined with advanced imaging technologies might have potential use in tumour localisation and radiation therapy planning of ovarian tumours. Monoclonal antibodies against MUC1 radiolabelled with γ -emitting radioisotopes, such as technetium-99m and indium-111, have been successfully used for the radioimmunological diagnosis of various malignant disease.^{56,57} For therapeutic purposes, monoclonal antibodies against the mucins or cancer-specific glycans present on these mucins can be conjugated with radionuclides or cytotoxins (figure 2). Binding of these antibodies or their derived forms to target mucins can induce their internalisation and intracellular retention of the pharmaceuticals or cytotoxins resulting in cytotoxicity. Non-internalising antibodies can be used to specifically eradicate tumour cells by targeting cytotoxic radionuclides. Several mucin-based immunoconjugates have been tested in preclinical and clinical studies of ovarian cancer (table 2).^{58–71} Mucin antibodies have been used to target chemical cytotoxic agents to ovarian cancer cells. Antibody–cytotoxin conjugates, such as humanised CTM01 antibody (against MUC1) conjugated with calicheamicin had remarkable therapeutic efficacy, not only against drug-sensitive, but also against cisplatin-resistant ovarian tumour xenografts.⁶¹ Likewise, an antibody against MUC16 (3A5) conjugated with a cytotoxic drug had potential toxicity against tumour cells in vitro and in tumour xenograft models.⁶⁸

For radioimmunotherapy, monoclonal antibodies labelled with β -emitting radioisotopes such as copper-67, yttrium-90, or rhenium-188 are being used to irradiate the spreading tumour cells, while sparing the normal cells.^{58,72–74} Although radioimmunotherapy has been of limited clinical usefulness for treatment, mainly due to toxic side-effects, the approach holds greater promise for the treatment of ovarian cancer. Because of peritoneal involvement, intraperitoneal administration of radiolabelled antibodies can result in high dose accumulation and decreased non-target toxicity.⁷⁵ The therapeutic efficacy of radioimmunotherapy with the murine mono-clonal antibody HMFG1 (anti-human milk fat

globules that recognises MUC1) labelled with three different radionuclides (^{90}Y , ^{186}Re , and ^{131}I) was assessed in athymic BALB/c mice with intraperitoneally growing NIH:OVCAR-3 ovarian carcinoma xenografts.⁷⁶ Each of the three radiolabelled antibody preparations, when given intraperitoneally, caused significant delay in ascites formation and death. In a non-randomised clinical trial (phase I and II), intraperitoneal administration of ^{90}Y -muHMFG1 antibody after surgical debulking and chemotherapy led to 10-year survival of 70% compared with 32% in case-matched controls.⁵⁸ However, a single intraperitoneal dose of ^{90}Y -muHMFG1 after surgery did not increase survival or time to relapse in a phase III trial.⁵⁹ A retrospective analysis of this study later suggested that the intraperitoneal administration of ^{90}Y -muHMFG1 decreased the incidence of peritoneal recurrence but increased the incidence of extraperitoneal occurrence.⁶⁰ Antibodies directed against MUC16 have also been assessed for the radioimmunotherapy of ovarian cancer. The phase I and phase II trials have shown the potential of ^{131}I -labelled OC125 antigen-binding fragment as a therapeutic agent.^{65–67} MUC4 is expressed by the tumour cells of peritoneal effusions in 99% of patients with ovarian cancer, indicating its potential as a target for intraperitoneal radioimmunotherapy.⁵³

Mucins in the development of cancer vaccines

The development of tumour vaccines for therapy and prophylaxis after primary therapy has recently received substantial attention. Newer therapeutic vaccines are being developed with the intentions of treating primary tumours and preventing their recurrence. Tumour vaccines can be categorised into three types: antigen-based, antibody-based, and cell-based (figure 3). Antigen-based vaccines are targeted against a specific tumour antigen or a protein that is significantly overexpressed on tumour cells. In this approach, either the DNA that encodes the tumour antigen or the synthetic peptide is introduced into the patient. The DNA is taken up by the dendritic cells, processed, and presented on the surface as an MHC–antigen complex to activate cytotoxic T cells. The antibody-based vaccine approach uses monoclonal antibodies that can trigger potent antibody-dependent cellular cytotoxicity and T-cell response. Furthermore, antibodies against tumour antigens can induce anti-idiotypic antibodies that mimic the epitopes in tumour antigens and can trigger potent antitumour response. For the cell-based vaccines, either tumour cells (containing tumour antigens) taken from the same patient (autologous) or a different patient (allogeneic) or dendritic cells (from the patient) loaded with tumour antigens are reintroduced into the patient to stimulate the immune system. Several vaccine formulations, including peptide-based vaccines (small peptide sequences derived from tumour antigens), virus augmented vaccines, and carbohydrate or glycolipid vaccines are in clinical trials.⁷⁷ Therefore, another possible approach involves the use of mucins to develop cancer vaccines to boost immune responses in ovarian cancer.⁷⁸ The induction of potential antimucin responses is particularly useful in targeting tumours that overexpress mucin. To generate efficient antigen-based vaccines, immune adjuvants or carrier proteins, such as Bacille Calmette-Guerin and keyhole limpet haemocyanin are generally conjugated to the mucin peptides.

In a pilot study, a heptavalent vaccine containing MUC1 peptide conjugated with keyhole limpet haemocyanin and various mucin-derived carbohydrate epitopes, in combination with QS21 (a *Quillaja saponaria* saponin used as an immunological adjuvant), safely induced

antibody response in patients with ovarian cancer.⁶³ Preclinical research has also shown efficacy of DNA vaccines and has explained the immunological mechanism of their action.⁷⁹ DNA vaccines are easier to construct than peptide-based vaccines and can generate long-lasting immune responses. *MUC1* has been used as a cancer DNA vaccine in the mouse model and produces long-term growth suppression of tumours.⁸⁰ In a recent phase I clinical trial, autologous dendritic cells pulsed with mannan–MUC1 fusion protein were used to immunise and treat patients with advanced malignant disease, including ovarian carcinoma.⁶⁴ Mannan-conjugated MUC1 is rapidly targeted to mannose receptors on dendritic cells, endocytosed, processed, and presented on the dendritic-cell surface with MHC class I molecules. In a recent study, dendritic cells expressing a combined PADRE/MUC4-derived polypeptide DNA vaccine also induced multiple cytotoxic T-cell responses.⁸¹ Because MUC4 overexpression is present in most epithelial ovarian cancer, this strategy can be tested in preclinical and clinical trials. The potential of MUC16 and MUC1 to generate antibody-based vaccines has been assessed in several clinical trials (table 2). Although repeated intradermal doses of a MUC1 antibody, HMFG1, was safe and tolerable, therapeutically relevant titres of MUC1 antibodies were not produced in a recent study.⁶² By contrast, oregovomab, a modified murine antibody against MUC16, induced both humoral and cellular responses in several clinical trials in patients with ovarian cancer.⁶⁹ Survival was increased in patients that mounted T-cell responses towards MUC16.⁸² However, in a randomised, placebo-controlled study, oregovomab treatment lengthened the time to relapse in a small subpopulation only.⁷⁰

An alternative approach to generate an immune response against MUC16 involves the use of anti-idiotypic antibodies. ACA125 (abagovomab) is an anti-idiotypic antibody generated against the MUC16 antibody, OC125, which mimics the antigenic epitope of MUC16 and serves as a surrogate when given to patients. In phase I or II clinical trial, patients treated with ACA125 developed anti-anti-idiotypic antibodies (Ab3) and MUC16 antibodies, and the Ab3-positive patients survived for longer than others.⁷¹ In a recent phase I trial, long vaccination schedules (nine vs six injections) were more effective in generating humoral and cellular responses.⁸³ To improve the potency of the anti-idiotypic vaccination, preclinical studies have examined the usefulness of a fusion protein of ACA125 with interleukin 6. ACA125–interleukin 6 fusion protein resulted in an increased induction of Ab3 by stimulating ACA125-specific B cells.⁸⁴

Conclusion and perspectives

Diagnosis, treatment, and management of ovarian cancer are challenging. In dealing with the epithelial ovarian cancer, we need to achieve earlier detection and improved therapeutic outcomes. Great progress has been made in recent years in aetiology, clinical pathology, and treatment.

Mucins are important biomolecules for cellular homeostasis and protection of epithelial surfaces. These molecules respond to physiological and immunological changes in expression and protein modification. These changes in cancer have multiple implications and clinical significance. Changes to the expression of mucins in ovarian cancer might be exploited in diagnosis, prognosis, and treatment. MUC16 is already being used in the clinics

as the only serum marker for ovarian cancer. Other differentially expressed mucins can also be used for the same purpose or combined with MUC16 to improve sensitivity and specificity of the assay.

Data about the functional role of mucins (MUC1 and MUC4 in particular) suggest important roles in the pathobiology of cancer, and hence, their clinical significance needs to be investigated in ovarian cancer. Nonetheless, preliminary expression data suggest that mucins can be exploited for immunolocalisation and immunotherapy. Mucins can also be used for the targeted delivery of pharmaceutical agents. Vaccines targeting ovarian tumour-associated mucins are in development and might help eliminate non-resectable peritoneal metastases after surgical removal of primary ovarian tumours.

New approaches targeting mucins in ovarian cancer can be tested for the development of peptide-based or DNA-based vaccines against a broad range of epitopes to overcome tumour heterogeneity. As we improve our understanding of the molecular mechanisms of the biological action of mucins and their aberrant regulation, new interventions can be developed for ovarian and other cancers. Progress in mucin biology, antibody engineering, biophysics, and computational technology will likely improve disease outcomes in ovarian carcinoma and cancer in general.

Acknowledgments

The authors of the article are supported by the grants from Department of Defense OC 040110 and the National Institutes of Health CA 78590. We acknowledge Kristi L W Berger (Eppley Institute) for editorial assistance. We also would like to thank Parmender P Mehta for helpful suggestions.

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Search strategy and selection criteria

Data for this Review were identified by searching Medline, PubMed, and cross references from relevant articles with the terms “mucins”, “ovarian cancer”, “mucins and ovarian cancer”, “MUC1 or MUC4 or MUC16 or CA125 or MUC and ovarian cancer”, “ovarian cancer and diagnosis or prognosis or therapy”, “epidemiology and ovarian cancer”, “mucins and radioimaging or radioimmunotherapy or immunotherapy or vaccine(s), or targeted delivery and ovarian cancer”. The search was limited to articles published in English between January, 1985, and April, 2008, and preference was given to recently published articles and related reviews over old articles to limit the number of references.

Figure 1. Mucins in progression of ovarian cancer

During early events of transformation and later stages of cancer progression, there is a change in mucin expression profiles and their post-translational modifications (mucin switching) that might have a role in aberrant growth and invasion (reprogramming of cell signalling) of ovarian cancer cells (A), exfoliation of tumour cells (alteration of cell-cell/cell-extracellular matrix adhesion; B), or tumour-cell spheroid formation by homotypic interaction (C), immune suppression by phenotypic change of natural killer (NK) cells (D), or inhibiting the components of complement system (E), adhesion to mesothelial cells by formation of novel heterotypic adhesion (F), and invasion into parenchyma of secondary tumour site and establishment of the secondary tumour (G).

Figure 2. Mucin-based targeted therapy

Overexpression, multiplicity of epitopes, and cancer-associated post-translational modifications of mucins make them potential candidates for targeted therapeutics. Antibodies conjugated with radioisotopes or cytotoxic drugs (such as iodine-131-labelled OC125 [monoclonal antigen-binding fragment] or humanised CTM01 conjugated with calicheamicin) enable targeted delivery to ovarian cancer cells.

Figure 3. Mucin-based ovarian cancer vaccines in clinical trials

Antigen-based vaccine (A): MUC1 (G5)–KLH peptides are taken up by antigen presenting cells (APC), processed, and presented with MHCII molecules on the cell surface, the presented antigens are recognised by the antigen-specific T cells, leading to humoral immune response, binding of the antibody to the target tandem-repeat region of MUC1 might inhibit ligand-receptor interaction or generate antibody-dependent cellular cytotoxicity leading to cell death. Cell-based vaccine (B): Autologous dendritic cells (DC) are derived from peripheral blood monocytes pulsed in vitro with the tumour antigen (Mannan-MUC1 fusion protein [MFP]), antigens are endocytosed, processed, and presented by mature dendritic cells displaying MHC-TAA complex on the surface, which are infused back into the patients where they activate cytotoxic T lymphocytes (CTLs). Antibody-based vaccines (C): MUC16 antibody B43.13 is believed to bind to the secreted MUC16 and form a complex that is taken up by APC, processed, and presented on the cell surface, where it can activate TAA-specific CTLs, which recognise and kill tumour cells in an antigen-specific manner. Alternatively, murine monoclonal antibody against TAA (Ab1) is injected into mice to generate an anti-idiotypic vaccine, such as abagovomab (Ab2β), Ab2β is injected into patients, taken in by APCs and TAA+MHC are displayed on the cell surface, anti-idiotypic antibodies are directed against the idiotopes of TAA antibodies and thus serve as the surrogates of TAA, in patients antibodies against idiotype antibodies elicit humoral and cellular response and a subset of antibodies against these (Ab3) recognise the epitopes on TAAs. The Ab3 antibodies and the CTLs target tumour cells in a TAA-specific manner and provide the antitumour immune response.

Table 1

Expression profile of mucins in normal ovaries and subtypes of ovarian cancer

	Normal ovary		Subtype			Detection methods	
	Serous	Mucinous	Endometrioid	Clear cell			
MUC1 ³⁰⁻³³ *	+-	+	+	+	+	Immunohistochemistry, northern blot	
MUC2 ³⁰⁻³² †	-	+	+-	+-	+-	Immunohistochemistry, northern blot	
MUC3 ^{34,35} ‡	-	+	..	..	..	In situ hybridisation, oligonucleotide microarray	
MUC4 ^{17,30,34} ‡	+-	+	+	+	+	Immunohistochemistry, in situ hybridisation, northern blot	
MUC5AC ^{30,34} ‡	+-	+	+	+	-	Northern blot, in situ hybridisation	
MUC5B ³⁴ ‡	..	+	-	+	+	In situ hybridisation	
MUC16 ^{17,36,37} *	+-	-	+-	+-	+-	Immunohistochemistry, SAGE	
MUC13 ³⁵ ‡	-	+	..	..	..	Oligonucleotide microarray, PCR	
MUC17 ^{35,38} ‡	-	+	..	..	..	Oligonucleotide microarray, in situ hybridisation	

SAGE=serial analysis of gene expression. +=mostly detected; -=not detected; +=sometimes detected.

* Poor prognosis in ovarian cancer.

† Not associated with prognosis.

‡ Role in prognosis of ovarian cancer not reported.

Table 2

Mucin-based immune treatments for ovarian cancer

Immunoconjugate		Vaccines		
		Antibody based	Antigen based	Cell based
MUC1	⁹⁰ Y-labelled anti-MUC1 (phases I, II, and III) ^{58–60} CMB-401 (calicheamicin conjugated fully humanised MUC1 antibody; preclinical) ⁶¹	Idiotypic vaccination with anti MUC1 HMGF1 monoclonal antibody (phase I) ⁶²	MUC1-presenting immunogens (pilot study) ⁶³	MUC1 pulsed dendritic cells ⁶⁴
MUC16	¹³¹ I-labelled OC125 monoclonal antibody (phases I and II) ^{65–67} 3A5-VC-MMAE antibody (preclinical) ⁶⁸	MUC16 B43.13 monoclonal antibody vaccine (OvaRex; phase IIb) ^{69,70} Anti-idiotypic antibody ACA125 vaccine (abagovomab; phase I) ⁷¹	..	..