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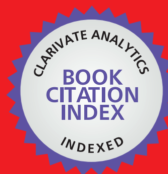

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The Role of MUC16 Mucin (CA125) in the Pathogenesis of Ovarian Cancer

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1. Introduction

The majority of epithelial ovarian carcinomas (EOCs) are derived from the ovarian surface epithelium (OSE). EOCs are the most lethal of all gynecological malignancies. Most patients present with advanced diseases in which tumor cells are disseminated throughout the peritoneal cavity. MUC16 serum level is a well-established marker for ovarian cancer (OC) progression and disease response to treatment. MUC16 is a high molecular weight, membrane associated-mucin, which is aberrantly expressed in advanced serous EOC. MUC16 is also expressed at the surface of corneal and respiratory epithelial cells, and the surface of female reproductive tract epithelium. It is however not expressed by the normal OSE. Like other membrane-bounded mucins, this glycosylated protein is primarily involved in the lubrification of epithelial luminal surfaces. MUC16 glycoprotein possesses unique structural motifs as compared with other membrane-bounded mucins. Its ectodomain is composed of a large heavily O-glycosylated N-terminus and a tandem repeat region with over 60 tandem repeats. MUC16 C-terminal domain (CTD) is composed of an extracellular unique region which contains a potential proteolytic cleavage site, a transmembrane domain and a short cytoplasmic tail with possible phosphorylation sites. MUC16 domains most likely have various functions resulting in activation of signalling pathways which regulate different tumor cell phenotypes. Indeed, recent functional studies have begun to uncover the unique role of MUC16 in the pathogenesis of OC. The present review will discuss the unique structure and functional roles of MUC16 in OC.

2. Ovarian cancer overview

OC is the fifth cause of cancer-related death in women in North America, the second most common gynecological cancer, and the leading cause of death from gynecological malignancies (Ozols *et al*, 2004). One in 78 women will develop OC during her lifetime (Jemal *et al.,* 2010). In 2010, nearly 22,000 new cases were estimated to occur in the United States and approximately 14,000 women are expected to die from this disease (Jemal *et al.,* 2010). Similar incidence and mortality has been observed in Canada, relative to the total population. Although survival rates approach 90% in OC patients diagnosed at early stage, most patients

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(~ 80%) are diagnosed with advanced diseases and metastases throughout the peritoneal cavity (Bast *et al.,* 2009). For these women, the 5-year survival rate is less than 30%.
Although OC may arise from all cell types composing the ovaries, EOC arising from the single-cell layer coelomic epithelium surrounding the ovaries, from postovulatory inclusion cysts or from the fimbriated end of the fallopian tube, are by far the most common (85-90% of all OC) (Ozols *et al*, 2004; Auersperg *et al.,* 2001; Landen *et al.,* 2008; Kindelberger *et al.,* 2007; Crum *et al.,* 2007 (2); Dubeau 2008; Kurman *et al.,* 2010). EOC presents substantial heterogeneity in terms of grade and histology. Most frequent EOCs divided into serous, mucinous, endometrioid and clear cell histotypes (Bast and al. 2009). Each histotype shows a distinctive gene expression and immunohistochemical profiling (Schwartz *et al.,* 2002; Ouellet *et al.,* 2005; Ouellet *et al.,* 2006; Ouellet *et al.,* 2008), and differs in the response to therapy (Bast *et al.,* 2009). Despite evidence of considerable heterogeneity in their histological phenotypes and molecular profiling (Bast *et al.,* 2009; Konstantinopoulos *et al.,* 2008; Soslow 2008), most cases of EOC are treated in a similar fashion.
Early detection of cancer patient remains an important objective in the field because over 70% of patients with EOC are diagnosed at late stage disease, with dissemination of tumor implants throughout the peritoneal cavity (Ozols *et al*, 2004; Aletti *et al.,* 2007; Goff *et al.,* 2000). Only 10-15% of these patients maintain a complete response after the initial therapy. The mean survival of patients that present with late stage disease, which is the case for most patients, is 39 months (Herzog 2004). Recurrence is associated with incurable diseases in most cases. The main obstacle to an effective treatment is the failure of the initial chemotherapy to eradicate a sufficient number of tumor cells to prevent disease recurrence. In this context, deficiency in the apoptotic cascade among tumor cells is a key hallmark of EOC.
The current standard treatment for advanced EOC consists of cytoreductive surgery and chemotherapy. Paclitaxel combined with platinum-based regimen is the standard first-line chemotherapy used for all patients with EOC (Colombo *et al.,* 2006). Serous EOC can be considered a chemosensitive neoplasm as most (80%) patients initially respond to the combination of paclitaxel and platinum-based drugs (McGuire *et al.,* 1996). However, 90% of the patients that initially responded will eventually develop chemotherapy-resistant diseases (Mano *et al.,* 2007). Although rarely curative, patients that do not respond to the first-line chemotherapy are given second-line and third-line regimens of chemotherapy in an attempt to prolong life and palliate symptoms.
Early on, MUC16 mucin has been recognized as a tumor-associated antigen because of its overexpression in EOC. Measurements of MUC16 serum level have been very useful over the years to monitor disease response or progression (Bast *et al.,* 2005). MUC16 is overexpressed in EOC, cleaved from the cell surface and detected into the peritoneal fluid and the blood. Since the characterization of the OC125 monoclonal antibody raised against the human ovarian cancer cell line OVCA433 in 1981 (Bast *et al.,* 1981; Bast *et al.,* 1983), a variety of MUC16-linked antibodies have been developed including VK8, M11 and 4H11 (Dharma Rao *et al.,* 2010; Nustad *et al.,* 2002). Except for 4H11 antibody, which recognizes an epitope in the noncleaved ectodomain of MUC16, other MUC16 antibodies bind to the glycosylated portion of the molecule. Measurement of serum MUC16 tumor antigen is an important part of the clinical management for EOC patients. Elevated levels of serum MUC16 are common in patients with advanced disease of serous histotype (~90%). It decreases to 50%-60% in patients with early stage OC. It was shown by several

groups that rising and falling levels of serum MUC16 correlate with progression and regression of the disease and this formed the basis for monitoring MUC16 serum levels for patient follow-up (Bast *et al.,* 1983; Canney *et al.,* 1984; Vergote *et al.,* 1987). However, up to 20% of patients with advanced EOC have normal serum level of MUC16. Furthermore, MUC16 levels can be elevated in various benign diseases including menstruation, first trimester pregnancy, endometriosis, adenomyosis, salpingitis, uterine fibroids, chronic renal failure or in inflammation of the pleura, peritoneum or pericardium (Bagdwell *et al.,* 2007; Xiaofang *et al.,* 2007). MUC16 is therefore not specific for EOC. MUC16, as a single modality, is not currently use for screening of EOC because of its lack of sensitivity and specificity.

Despite its recognized utility for the follow up of patients with EOC over the last three decades, the understanding of MUC16 structure became apparent only with the cloning of the gene in 2001. In addition, because of the lack of suitable cellular models, MUC16 functions have remained mostly unknown until very recently.

3. MUC16 structure

Although MUC16 was recognized as a high molecular weight glycoprotein a few years after the description of OC125 monoclonal antibody (Davis *et al.,* 1986), and its structure confirmed by subsequent studies (Lloyd *et al.*, 1997; Lloyd *et al.,* 2001), it took 20 years before the MUC16 gene could be cloned (Yin and Llyod, 2001; O'Brien *et al.,* 2001; Yin *et al.,* 2002). The gene is located on chromosome 19p13.2 (Yin and Lloyd, 2001). The deduced amino acid sequence of MUC16 demonstrated that it resembles other membrane-bounded mucins with high serine, threonine and proline content. With a molecular weight of > 2 MDa, MUC16 is the largest membrane-bounded mucin known to date (O'Brien *et al.,* 2001; O'Brien *et al.,* 2002). This glycoprotein is composed of three major domains: an N-terminal domain, a large multiple repeat domain (up to 60 tandem repeats of 156 amino acids each) and a C-terminal domain (O'Brien *et al.,* 2001) (Fig. 1). The N-terminal domain and the repeat domain are heavily glycosylated with both O- and N-linked oligosaccharides (Kui *et al.,* 2003). The C-terminal domain is composed of an extracellular domain with sea urchin sperm protein, enterokinase and agrin (SEA) domains, a transmembrane domain to anchor the protein to the cellular membrane and a short cytoplasmic tail (31 amino acids) with potential serine, threonine and tyrosine phosphorylation sites. The phosphorylation of MUC16 cytoplasmic tail has been associated with its secretion (Fendrick *et al.,* 1997). The secretion of MUC16 is stimulated by epidermal growth factor (EGF) or tyrosine phosphatases (Konishi *et al.,* 1994). Its shedding is decreased by glucocorticoids (Karlan *et al.,* 1988).

Human MUC16 differs from other mucins by having 16 SEA domains located near the membrane-spanning sequence. Other membrane-bounded mucins usually have a single SEA domain (Duraisamy *et al.,* 2006). SEA domains consist of about 120 amino acids. Sequence analysis of MUC16 SEA modules showed that they display some sequence variability. The second MUC16 SEA domain however is relatively conserved and most closely resembles the SEA domain found in other mucins. It may therefore provide the preferential cleavage site, like as in MUC1 and MUC3, which allows release of MUC16 from the cell surface. This, however, remains to be confirmed. Unlike MUC1 and MUC4, MUC16 lacks an EGF-like domain. Through their EGF-like motif located at C-terminal domain (extracellular portion), MUC1 and MUC4 bind to growth factor receptor tyrosine kinases (RTKs) such as erbB family and fibroblast growth factor receptor 3 (FGFR3) (Li *et*

al., 2001; Ren *et al.*, 2006; Schroeder *et al.*, 2001; Pochampalli *et al.*, 2007). The formation of heterodimer with RTKs causes cross-phosphorylation of their respective cytoplasmic domain leading to the activation of various signaling pathways (Bafna *et al.*, 2010). Because MUC16 lacks an RTK binding motif in its C-terminal domain, it is not clear whether MUC16-induced signaling is affected by RTKs although, as mentioned above, MUC16 release from the cell is stimulated by EGF. Consistent with the lack of an RTK binding motif, the intracellular interaction between MUC16 and β-catenin is not affected by EGF (Comamala *et al.*, 2011). MUC16 cytoplasmic tail contains a polybasic sequence of amino acids (RRRKK) which is predicted to bind to the ezrin/radixin/moesin (ERM) family of proteins (Fig. 2). This motif is not found in MUC1 and MUC4. The ERM proteins can interact with numerous membrane-associated proteins and the actin cytoskeleton. Consistently, MUC16 has recently been shown to interact with E-cadherin and β-catenin, and causes alteration in the actin cytoskeleton (Comamala *et al.*, 2011). However, it remains unclear whether MUC16/β-catenin and MUC16/E-cadherin interaction is mediated through the ERM motif of the MUC16 cytoplasmic tail. MUC1 cytoplasmic tail has been shown to bind to β-catenin and a serine-rich SXXXXXSSL motif in MUC1 is responsible for this interaction *in vitro* (Yamamoto *et al.*, 1997; Wen *et al.*, 2003; Huang *et al.*, 2005). This motif is notably absent in MUC16. Interestingly however, the binding of MUC1 to β-catenin in cells was independent of the serine-rich motif (Huang *et al.*, 2005). These observations suggest that MUC16 interaction with β-catenin is mediated by an indirect mechanism, probably through another protein. The positively charged R-K rich region of MUC16 cytoplasmic tail also constitutes a putative nuclear localization motif (Bafna *et al.*, 2010). Whether MUC16 cytoplasmic tail does indeed localize to the nucleus, as MUC1 cytoplasmic tail does (Wen *et al.*, 2003), remains to be determined. MUC1 nuclear localization suggests that it is cleaved and released from the membrane and traffic from the membrane to the cytoplasm and the nucleus.

Although MUC16 shares some structural similarities with other membrane-bounded mucins, it possesses many unique features suggesting that its signaling capabilities and functions may differ from other mucins.

4. Expression of MUC16 in normal tissues and ovarian tumors

Mucins are normally expressed by epithelial cells where they play a protective role. The extensive glycosylation of mucins provides a hydrophilic environment ideal for hydration and lubrication of epithelia. MUC16 is expressed at low levels in the normal airway epithelium but levels can increase in some chronic conditions such as cystic fibrosis (Hattrup *et al.*, 2008; Davies *et al.*, 2007; Gronowitz *et al.*, 2003). MUC16 is expressed at the apical surface of the ocular and conjonctival epithelium where it is part of the glycocalyx protecting corneal cells from bacterial infections and dryness (Argueso *et al.*, 2003; Blalock *et al.*, 2007). MUC16 is also found in lacrimal glands (Jäger *et al.*, 2007). Immunohistochemistry of human tissues using the OC125 antibody detected MUC16 expression in other epithelia such as the fetal coelomic epithelia and its derivatives such as Müllerian duct, fallopian tube, endometrium, and endocervix. MUC16 is also expressed by mesothelial cells of the peritoneum, pleura and pericardium (Kabawat *et al.*, 1983; Nap 1998). However, using OC125 or 4H11 antibodies, MUC16 expression is not found in normal adult colon, rectum, cervix, small intestine, liver, pancreatic ducts, spleen, kidney, skin and ovaries (Rao *et al.*, 2010).

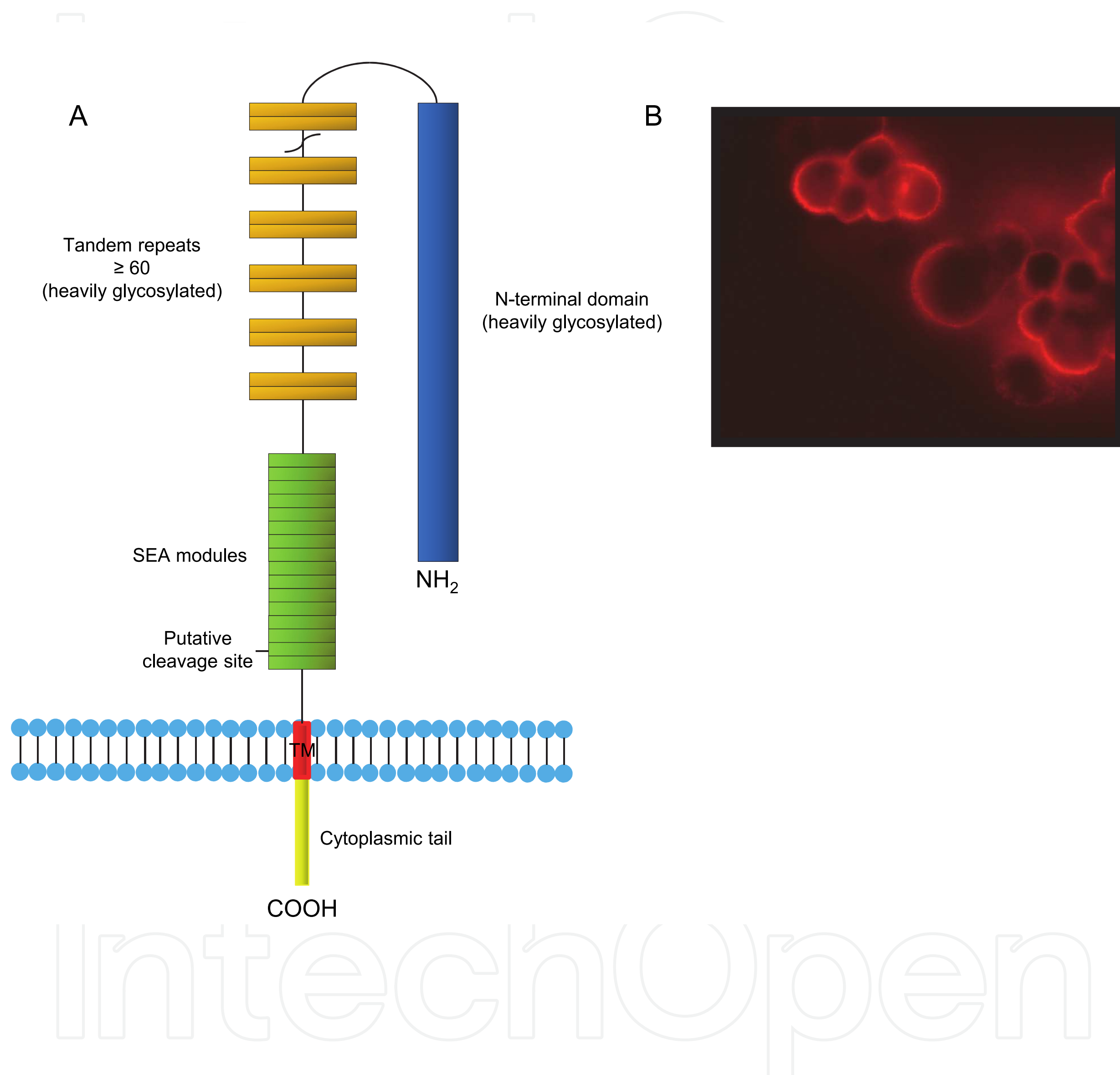

Fig. 1. Schematic structure of MUC16 mucin. A. The major domains of MUC16 include the N-terminal domain, the tandem repeat domain and the C-terminal domain. The SEA modules contain a putative proteolytic cleavage site which divides MUC16 in two subunits. The extracellular larger subunit consists of the N-terminal (> 12,000 a.a.) and tandem repeat domains (156 a.a. each), and are heavily glycosylated. The smaller subunit contains SEA domains, a transmembrane domain (TM) and the cytoplasmic tail (31 a.a.). B. MUC16 is usually expressed at the apical surface of normal epithelial cells. In EOC cells, this pattern of expression is lost and MUC16 is expressed through the entire surface of the tumor cells. The micrograph represents OVCAR3 cells probed with M11 antibody.

Fig. 2. Sequence of MUC1, MUC4 and MUC16 cytoplasmic tails. The intracellular sequence of the different mucins is shown along with protein interaction sites. MUC1 is the best characterized mucin. MUC1 cytoplasmic tail interacts with c-Src, GSK3β, PCKδ, β-catenin, p53, ERα, HSP70/90, Grb2, AP-2. Proteins with kinase activity are in blue whereas those without kinase activity are in yellow. HSP70 binds to MUC1 cytoplasmic tail in the same region as β-catenin. HSP90 binding to MUC1 depends on c-Src-induced Y-46 phosphorylation. MUC16 cytoplasmic tail has an ERM motif for potential interaction with the cytoskeleton. Both MUC1 and MUC16 contain a potential nuclear localization signal motif. MUC4 has no known interaction binding partners.

The expression of MUC16 in EOC tissues varies according to the histotype. Using tissues arrays, Hogdall *et al.*, reported that MUC16 was expressed by 85% of serous, 65% of endometrioid, 40% of clear cell and 36% of undifferentiated adenocarcinomas, but by only 12% of mucinous cancers (Hogdall *et al.*, 2007). Limited expression of MUC16 in mucinous EOC has also been reported by other groups (de la Cuesta *et al.*, 1999). These authors also showed that MUC16 tissues expression was significantly correlated with the FIGO stage but not with the histological grade (Hogdall *et al.*, 2007). In another study using tissues arrays, Rao *et al.*, found that 56%-66% of serous high grade EOC expressed MUC16 depending on the antibody used (OC125 vs 4H11) (Rao *et al.*, 2010). Other studies have also shown the lack MUC16 tissues expression in 15% to 25% of serous EOC (Lu *et al.*, 2004; Rosen *et al.*, 2005; Breitenecker *et al.*, 1989). MUC16 was also found to be expressed in a small percentage (3%-4%) of invasive breast carcinomas and 13% of lung carcinomas (Rao *et al.*, 2010).
Because MUC16 is expressed in a limited subset of early stage OC, in other types of cancers and in a number of benign conditions, its serum level is neither a sensitive nor a specific marker to detect early diseases. However, as mentioned previously, it is a useful marker to monitor response to treatment. In patients who reached complete response after standard primary treatment, MUC16 nadir serum values were associated with a

significantly longer progression-free survival (PFS) and overall survival (Rustin *et al.*, 1996; Krivak *et al.*, 2009; van Altena *et al.*, 2010). Pretreatment MUC16 serum level is an independent predictor of PFS in patients with advanced EOC who received a standard chemotherapy regimen (Zorn *et al.*, 2009). In contrast, high MUC16 expression in EOC tissues has inconsistently been associated with overall survival. de la Cuesta *et al.*, found that, in a cohort of 50 EOC samples, patients with high tissue expression of MUC16 had a higher risk of death compared to patients with no expression (de la Cuesta *et al.*, 1999). However, in a much larger cohort of 778 EOC samples, Hogdall *et al.*, showed that late-stage patients that lacked MUC16 tissue expression had a significantly poorer survival (Hogdall *et al.*, 2007). In addition, MUC16 expression had no prognostic value in early stage EOC (Hogdall *et al.*, 2007). Because the immunohistochemical detection of tissues MUC16 was based on antibodies that recognize glycosylated epitopes in the tandem repeats in these studies, the expression of a cleaved MUC16 lacking the N-terminal and the tandem repeats domains could not have been detected. Furthermore, the fact that we recently shown that a MUC16 construct consisting of the last C-terminal 283 amino acid was sufficient to promote tumorigenicity (Thériault *et al.*, 2011), is not inconsistent with the observation that late-stage EOC lacking MUC16 (as assessed by immunohistochemistry) is associated with a worse prognosis.

5. MUC16 roles in the initiation and progression of ovarian cancer

Membrane-bounded mucins such as MUC1 and MUC4 are multifunctional molecules. Their large extracellular, heavily glycosylated domain promotes adequate hydration and lubrification of epithelia, and serve as a protective barrier with anti-adhesive properties. On the other hand, through their cytoplasmic tail, they activate various signaling pathways.

MUC16 is also seen as a multifunctional molecule with different domains involved in specific functions. Both secreted and membrane-bounded MUC16 have been shown to interact with galectin-1 (Seelenmeyer *et al.*,, 2002). The MUC16 C-terminal domain (last 1148 amino acids) appears to be sufficient for binding to galectin-1 but this interaction requires O-linked oligosaccharide chains which are found in the repeats of the MUC16. The biological significance of this interaction remains unclear but the cell surface recruitment of galectin-1 has been associated with processes such as regulation of cell adhesion (Perillo *et al.*, 1998). MUC16 facilitates cell-cell adhesion through its binding with mesothelin (Rump *et al.*, 2004; Gubbels *et al.*, 2006). The binding site for mesothelin on MUC16 is likely located in the 156 amino acid tandem repeats of the molecule (Gubbels *et al.*, 2006). MUC16 binds primarily to the N-terminus of the extracellular domain of mesothelin (residues 296-359) (Kaneko *et al.*, 2009). Mesothelin is a glycoprotein normally expressed on the mesothelial cells lining the peritoneal cavity (Chang *et al.*, 1996), and by ovarian tumor cells and mesotheliomas (Rump *et al.*, 2004). Mesothelin-MUC16 interaction could facilitate homotypic and heterotypic cell-cell adhesion and peritoneal metastasis of ovarian tumors through the adhesion with mesothelial cells. This is consistent with our recent observation that MUC16 knockdown abolished homotypic cell-cell adhesion (Comamala *et al.*, 2011). MUC16 knockdown also promotes EOC cell motility and invasiveness (Comamala *et al.*, 2011). By regulating cell adhesion, cell motility and invasiveness, the extracellular portion of MUC16, through its interaction with galectin-1 and mesothelin, may thus play an important role in metastasis.

MUC16 possesses immunosuppressive properties. Patankar *et al.*, reported that natural killer (NK) cells incubated with soluble MUC16 exhibited a 50–70% decrease in the lysis of tumor cells (Patankar *et al.*, 2005). MUC16-expressing EOC cells are also protected from lysis by primary NK cells (Gubbels *et al.*, 2010). Both soluble and membrane-bound MUC16 thus appear to be potent inhibitors of NK cells response *in vitro*. MUC16 downregulates CD16 expression in NK cells found in peritoneal fluids of patients with EOC (Patankar *et al.*, 2005; Belisle *et al.*, 2007). The secreted MUC16 binds to NK cells, B cells and monocytes via Siglec-9, a receptor found on immune cells that inhibits the NK cell response (Belisle *et al.*, 2010). The high levels of secreted MUC16 found in ascites may be one of the factors contributing to the immunosuppressive properties of ascites.

MUC1 and MUC4 mucins have been shown to promote the transformation of fibroblast cells. For example, when the C-terminal portion of MUC1 was stably transfected into 3Y1 fibroblast cells, soft agar colonies and subcutaneous tumors in nude mice were readily obtained (Li *et al.*, 2003). The transforming potential of MUC16 has not been reported yet but limited data from our laboratory showed that stable transfection of MUC16 C-terminal portion (extracellular unique region, transmembrane domain and full-length cytoplasmic tail) into normal ovarian cells failed to immortalized these cells as well as HFL-1 human fibroblast lung cells (Thériault, unpublished data). Recently, ectopic expression of MUC-16 C-terminal domain has been shown to increase tumorigenicity of SKOV3 ovarian cancer cell line in a xenograft mouse model (Thériault *et al.*, 2011). Deletion of the cytoplasmic tail completely abrogated this effect demonstrating that the enhanced tumorigenicity is mediated by interaction of the cytoplasmic tail with intracellular signaling molecules. Consistent with these results, single-chain antibody-mediated knockdown of cell surface MUC16 completely abrogated the formation of colonies in soft agar and subcutaneous tumors with OVCAR3 cells suggesting that MUC16 could be indeed an oncogene (Thériault *et al.*, 2011). Although MUC1 and MUC4 affect tumor progression through the interaction of their cytoplasmic tail with various intracellular signaling molecules (for review, see Bafna *et al.*, 2010), there is very limited data available on the signaling pathways activated by MUC16 cytoplasmic tail. Data from our laboratory suggest that the expression of anti-apoptotic proteins Bcl-2 and Bcl-XL and pro-apoptotic protein Bax is not affected by ectopic expression of MUC16 C-terminal domain (Matte *et al.*,, unpublished data). This observation contrasts with those of Raina *et al.*, which showed that stable transfection of MUC1 in rat 3Y1 fibroblast upregulates Bcl-XL but not Bcl-2 expression (Raina *et al.*, 2004). Growth factors induce tyrosine phosphorylation of MUC1 cytoplasmic tail (Ren *et al.*, 2006). This phosphorylation increases the binding of MUC1 to β-catenin and induces the translocation of MUC1 and β-catenin to the nucleus (Ren *et al.*, 2006). The dysregulation of β-catenin signaling contributes to the transformed phenotype of various cancers (Huang *et al.*, 2005). GSK3β phosphorylates β-catenin and targets it for ubiquitination and degradation (through β-Trcp, an E3 ubiquitin ligase) whereas the inhibition of GSK3β kinase activity results in the translocation of β-catenin from the cytosol to the nucleus where it acts as a transactivator of transcription. MUC1 increases the cytoplasmic and nuclear localization of β-catenin by inhibiting GSK3β-mediated phosphorylation and degradation of β-catenin (Huang *et al.*, 2005). Whether MUC16 could play a role similar to MUC1 is unknown. MUC16 cytoplasmic tail however lacks the β-catenin binding site. Nonetheless, MUC16 was shown to interact with β-catenin (Comamala *et al.*, 2011). In addition, MUC16 knockdown induces β-catenin

relocalization from the cell membrane to the cytoplasm (Comamala *et al.,* 2011) and increases GKS3β activity (Comamala, unpublished data). It is thus possible that by regulating GKS3β activity, MUC16 regulates β-catenin subcellular localization/degradation. Importantly, β-catenin relocalization in MUC16 knockdown cells is associated with increase cell motility, migration and invasiveness *in vitro* (Comamala *et al.,* 2011). So far, there is no evidence that MUC16 cytoplasmic tail co-localizes with β-catenin in the cytoplasm or the nucleus. How does MUC16 regulates GKS3β activity is also not known. GKS3β has been shown to bind directly to MUC1 cytoplasmic tail and phosphorylates serine in a DRSP site adjacent to that for the β-catenin interaction (Li *et al.,* 1998). This GKS3β target motif is not present in MUC16 cytoplasmic tail and it has not been established yet whether MUC16 binds to GKS3β. The binding of GKS3β to MUC1 appears to be regulated by the phosphorylation of MUC1 by Src family members (Singh *et al.,* 2006). MUC16 cytoplasmic tail is phosphorylated by EGFR activation and its phosphorylation promotes the release of the extracellular domain. Other consequence of this phosphorylation event has not been yet reported.

MUC1 and MUC4 have been implicated in the regulation of cell growth through their interaction with tyrosine kinase growth factor although these mucins act through different mechanisms (Bafna *et al.,* 2010). MUC1 interacts with ErbB1 through its cytoplasmic tail and increases cell proliferation via the activation of ERK pathway (Jepson *et al.,* 2002). MUC4 probably interacts with ErbB2 through its extracellular domain which leads to the activation of ERK and Akt pathways to promote cell growth (Carraway *et al.,* 2007). MUC16 was also recently shown to affect the growth characteristics of ovarian cancer cells (Thériault *et al.,* 2011). Although the OVCAR3 cell growth rate was not affected by MUC16 knockdown, knockdown cells reached a stationary growth phase in a shorter time. There was no appreciable difference in spontaneous apoptosis between the MUC16 knockdown cells and control cells. Conversely, stable expression of the C-terminal domain into MUC16 negative SKOV3 cells prolonged anchorage dependent growth before they reached the stationary phase. Deletion of the cytoplasmic tail completely abrogated the effect of the MUC16 C-terminal domain on cell growth. It is not known how MUC16 affects tumor cell growth. Stable expression of the MUC16 C-terminal domain in SKOV3 cells did not alter the expression or phosphorylation of EGFR. Although these observations do not rule out the involvement of receptor tyrosine kinase, other partners are probably required to modulate cell growth.

A recent study showed that MUC16 confers protection against genotoxic agents such as cisplatin in p53 null ovarian cancer cells (Boivin *et al.,* 2009). Single-chain antibody-mediated downregulation of MUC16 sensitized the MUC16 overexpressing OVCAR3 cell line to cisplatin but not to taxol. Conversely, ectopic expression of MUC16 C-terminal domain increased SKOV3 cell line resistance to cisplatin. The downregulation of MUC16 in OVCAR3 cells activates the PI3K/Akt pathway (Comamala *et al.,* 2011). The authors also reported that MUC16 knockdown in these cells decreased FOXO3a nuclear localization. FOXO3a function is controlled in part by activation of the Akt pathway. Akt phosphorylates FOXO3a, resulting in binding of FOXO3a to 14-3-3 proteins and retention of FOXO3a in the cytoplasm. In contrast, dephosphorylation of FOXO3a induces its nuclear localization where it transactivates gene expression (Nemoto *et al.,* 2002). FOXO3a modulates the expression of several genes that regulate the cellular response to stress at the G2-M checkpoint. The growth arrest and DNA damage response gene Gadd54a is a target of FOXO3a that

mediates part of FOXO3a's effects on DNA repair (Tran *et al.,* 2002). Thus, preventing the nuclear localization of FOXO3a contributes to the apoptotic response to genotoxic drugs. These data suggest that MUC16 knockdown sensitizes tumor cells to genotoxic drugs by activating Akt which in turn prevents FOXO3a nuclear localization. The knockdown of MUC1 has also been reported to sensitize carcinoma cells to apoptosis induced by genotoxic agents (Yin *et al.,* 2004; Ren *et al.,* 2004).

EOC is a highly metastatic disease which primarily metastasizes to the serosal cavities while dissemination through the vasculature is unusual (Naora *et al.,* 2005). During the progression to a metastatic phenotype, carcinoma cells undergo morphological changes, become motile and acquire the ability to migrate and invade to establish secondary tumors at distant sites. This epithelial to mesenchymal transition (EMT) is characterized by coordinated molecular and cellular changes including a reduction in cell-cell adhesion, the loss of apical-basolateral polarity, the loss of epithelial markers and the gain of mesenchymal markers (Vergara *et al*, 2010; Hugo *et al*, 2007). EMT is an important physiological process during embryogenesis and wound healing, but also a key step in cancer metastasis (Radisky, 2005). EMT is a necessary step towards metastatic tumor progression during detachment of tumor cells from the primary tumor site and attachment to metastatic sites. A key feature of EMT is the switch from E-cadherin expression at the cell surface to N-cadherin which promotes the interaction with stromal components (Cavallaro *et al.,* 2004). EMT results in enhanced cell motility and invasion. MUC16 was recently shown to be an important regulator of EMT in OC cells (Comamala *et al.,* 2011). Using a MUC16 knockdown OC cell model, the authors showed that downregulation of MUC16 cell surface expression prevents homotypic cell aggregation, enhances disruption of cell-cell junctions and increases cell motility and invasiveness. These effects were associated with the loss of epithelial markers such as E-cadherin and cytokeratin-18 and gain of mesenchymal markers such as N-cadherin and vimentin in knockdown cells. These data suggest that MUC16 is involved in the metastatic process. As mentioned previously, MUC16 knockdown induces an intracellular relocalization of E-cadherin. It is possible that the binding of MUC16 to E-cadherin complexes results in the surface localization of E-cadherin, which mediates cell contact and suppression of cell migration. Conversely, in the absence of MUC16, E-cadherin relocalizes in the cytoplasm, which abolishes its ability to promote cell contact formation. The cytoplasmic domain of E-cadherin binds to β-catenin, which forms complexes with α-catenin (Ozawa *et al*, 1990), actin (Adams *et al*, 1996), p120 (Staddon *et al*, 1995), EGFR (Hoschuetzky *et al*, 1994), and other proteins. It is possible that by forming a complex with E-cadherin and/or β-catenin, MUC16 re-distributes EGFR and consequently modulates its signaling pathway. Although expression of MUC16 C-terminal domain in SKOV3 cells does not affect EGFR phosphorylation, MUC16 knockdown activates EGFR resulting in increased activation of Akt, ERK1/2 and MMP-2 and MMP-9 (Comamala *et al.,* 2011). Activation of the MAPK-ERK pathway has been shown to upregulate MMP-9 and to enhance cell migration (Suyama *et al*, 2002). Akt activation has been associated with induction of EMT in carcinoma cells (Grille *et al*, 2003; Yan *et al*, 2009). In summary, the early steps in ovarian tumor metastasis involve shedding of the primary tumor through alterations of cell adhesive properties into ascites to form free floating cells or multicellular aggregates. Tumor cells from the primary site express MUC16, display a more epithelial phenotype and express E-cadherin. Shedding from the primary tumor site involves the loss of MUC16 and E-cadherin expression and the gain of mesenchymal markers leading to increased motility and loss of

adhesive properties. Following this EMT, floating tumor cells revert to an epithelial phenotype and express MUC16 leading to adhesion to mesothelial cells via MUC16/mesothelin interaction and the formation of tumor implants in the peritoneal cavity.

MUC16 has been shown to alter tumorigenicity and metastasis of EOC cells (Thériault *et al.*, 2011). MUC16 knockdown inhibited cell growth in soft agar and abolished the formation of subcutaneous tumor nodule. Conversely, the MUC16 C-terminal domain appears to be sufficient to enhance *in vitro* and *in vivo* tumorigenicity, and promote dissemination of tumor cells throughout the peritoneal cavity of SCID mice. Importantly, deletion of MUC16 cytoplasmic tail completely abolished these effects. Although the mechanism by which MUC16 affects tumorigenicity and metastasis is unknown, this study suggests that MUC16 plays a critical role in the progression of EOC.

Although MUC16's functions are beginning to be elucidated in EOC cells, the normal function of MUC16 is for the most part unknown. As mentioned previously, it is expressed by various tissues, notably the conjonctiva and the lachrymal glands, were it can play a protective role against bacterial infection. Its expression in fallopian tube and endometrium suggests a role in reproduction. However, knockout mice have been shown to display a normal phenotype by 1 year of age demonstrating that MUC16 is not required for mouse development and reproduction (Cheon *et al.,* 2009). Consistent with these data, MUC1 null mice have normal fertility and development (Spicer *et al.,* 1995). One explanation that has been evoked for the lack of phenotype for MUC16 and MUC1 knockout mice is that functional redundancy can compensate for the loss of other mucins.

6. Conclusions and future directions

Since its discovery in the late 1970s, MUC16 glycoprotein has been recognized as a useful clinical biomarker in advance diseases. However, accumulating evidence suggests that MUC16 is more than a biomarker for disease progression; MUC16 contributes to the pathogenesis and progression of EOC. MUC16 appears to regulate cell survival, cell motility, invasiveness and tumorigenicity in EOC cells. These phenotypic effects are also shared by other membrane-bounded mucins such as MUC1 and MUC4. However, the underlying mechanisms responsible for the biological functions are likely to differ between mucins because of their structural differences, notably in their cytoplasmic tail. Although progress has been made regarding the role of MUC16 in tumor progression, the signaling pathways activated by its cytoplasmic tail are mostly unknown. The functional role of MUC16/β-catenin and MUC16/E-cadherin interactions is not known. Further studies are needed to understand the contribution of these interactions in tumor progression. Identifying the signaling molecules activated by MUC16 and elucidating their contribution to EOC progression will be critical in the near future as MUC16 may represent a target for EOC treatment.

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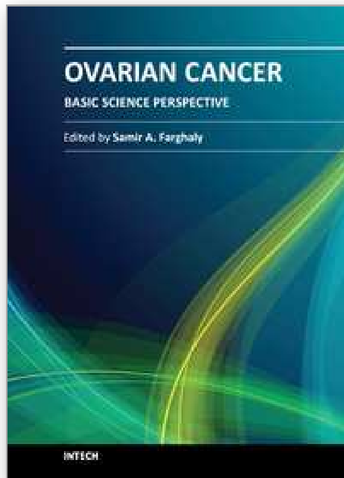

Ovarian Cancer - Basic Science Perspective

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Worldwide, Ovarian carcinoma continues to be responsible for more deaths than all other gynecologic malignancies combined. International leaders in the field address the critical biologic and basic science issues relevant to the disease. The book details the molecular biological aspects of ovarian cancer. It provides molecular biology techniques of understanding this cancer. The techniques are designed to determine tumor genetics, expression, and protein function, and to elucidate the genetic mechanisms by which gene and immunotherapies may be perfected. It provides an analysis of current research into aspects of malignant transformation, growth control, and metastasis. A comprehensive spectrum of topics is covered providing up to date information on scientific discoveries and management considerations.

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