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BREAKTHROUGHS AND VIEWS

Mucin Functions and Expression in Mammalian Reproductive Tract Tissues

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Reproductive tract tissues must provide protection from microbial infection and enzymatic assault. In addition, these mucosa support gamete transport and, in the case of the uterus, growth and development of the embryo. Sperm display various adhesion-promoting molecules on their surface (1, 2). These adhesion molecules not only facilitate attachment to eggs, but also may promote sperm adhesion to components of somatic cells, including those of the reproductive tract (3). Nonetheless, sperm manage to traverse the male reproductive tract and a subset also navigates the female reproductive tract to the oviduct where fertilization occurs. Copulation results not only in the introduction of sperm, but also a significant microbial challenge in the female reproductive tract. Reproductive tract infection severely impairs reproductive success at both early and later stages of pregnancy (4, 5). Therefore, this microbial challenge must be met and overcome prior to the time the embryo descends into the uterus for implantation.

Female reproductive tract tissues are active sites of cytokine production (6) and display the ability to recruit various cells of the immune system in relationship to the hormonal status of the animal (7, 8). Following fertilization, high levels of proinflammatory cytokines are produced (9, 10). In addition, large numbers of macrophage-like cells extravasate into the uterine lumen where they appear to phagocytize residual sperm, bacteria and other debris (11, 12). Microbial adhesion and infection occurs quickly relative to the time course in which cellular immune responses of the reproductive tract mucosa occur (13, 14). Thus, it seems important to minimize microbial interactions with reproductive tract tissues until the appropriate host defense responses can be mounted. Like other mucosa, the reproductive tract is coated with a thick coat of mucin glycoproteins that affords a physical barrier to enzymatic and microbial attack. In the discussion below, the types of mucin glycoproteins expressed by reproductive tract tissues will be considered as they may function as general barrier molecules. In addition, specialized functions and patterns of regulation of mucins will be discussed in the context of embryo fertilization, transport and implantation.

MUCIN FUNCTIONS

Mucin glycoproteins are very large, highly hydrated structures. As such, they can function as lubricants and prevent dehydration of lumenally-disposed cell surfaces (15, 16). A number of proteins not classically thought of as mucins, e.g., LDL receptor, contain regions heavily substituted with O-linked oligosaccharides. The dense packing of the oligosaccharides protect these regions of proteins from proteolytic attack (15). In classic mucins this principle is extended. Virtually all of the protein core of soluble mucins and the extracellular domain of transmembrane mucins are substituted with O-linked oligosaccharides making them extremely resistant to proteolysis.

Mucins have classically been attributed the role of a protectant against bacterial invasion and infection. Bacterial access to mucosa comes from the external environment via ingestion, respiration or coital activity. Given the diversity of the organ systems involved, an underlying characteristic holds firmly: a luminal epithelial layer expresses and is covered by a thick gelatinous mucin layer in which bacteria are trapped (17, 18). Subsequently, immunological responses, such as phagocytosis and outflow from the organ system, neutralize and remove bacteria from the host. This process is quite evident in the respiratory system where ciliary beating removes mucin-trapped bacteria from the bronchial passages and trachea and are released

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as sputum (18). Given the extreme diversity of bacteria present in the environment an equally diverse method of entrapment is necessary. In most bacteria thus far examined, bacterial proteins (adhesins) act as receptors for carbohydrate epitopes expressed on mucins. Often these interactions occur between selective sulfated or sialylated carbohydrate moieties. For example, in such diverse tissues as vagina, mouth and small intestine, *E.coli* Type I, S and K88 fimbriae all recognize carbohydrate structures expressed on mucins as their cognate ligands (19-21). In addition, in the respiratory system both *Staphylococcus aureus* and *Pseudomonas aeruginosa* have been shown to bind to mucin carbohydrates (22, 23). More recently, ulcer-causing bacteria, *Helicobacter pylori*, have been shown to be inhibited from binding to acidic glycosphingolipids on gastric epithelial cells by gastric sulfomucins (24). Even with the multitude of bacteria attempting colonization within the host, the diversity of carbohydrate chains expressed on mucin proteins severely limits the ability of different bacteria to escape capture. The method by which transmembrane mucins protect cells from bacterial infection is less clear since these molecules would be expected to promote bacterial attachment to the mucosal surface. It is possible that binding to cell surface mucins still prevents binding to more proximal carbohydrate-bearing cell surface components, e.g., most glycoprotein receptors and gangliosides. It also is possible that bacterial binding stimulates release of mucin ectodomains thereby preventing surface adherence.

The large, extended structures of cell surface mucins also limit accessibility to other cell surface components. The abundance of cell surface mucins as well as the number of tandem repeat motifs play important roles in such activities (25, 26). Studies in which the number of tandem repeats of MUC1/episialin or sialomucin complex have been systematically reduced indicate that a structure minimally extending 50-200 nm from the cell surface is required to present an effective barrier. The presence and structure of oligosaccharide chains also play an important role in this regard. Inhibitors of O-linked oligosaccharide assembly cause production of mucin glycoproteins with truncated or aberrant structures (27). Uterine epithelial cells treated with such inhibitors display increased accessibility of apically disposed cell surface components to both carbohydrate ligands and enzymes (28). Similarly, it is believed that the propensity of many tumor cells to express high levels of mucins aids in their protection from the host immune system (16, 29, 30). In addition to sterically preventing immune cells from attacking the tumor cell surface, mucins also may repress immune cell activities or stimulate apoptosis of immune cells (31-33).

From the above, it can be reasoned that one result of high level mucin expression is the creation of an enzymatically resistant, non-adhesive cell surface. In fact, mucins limit access to host cell receptors and severely impair cell-cell and cell-extracellular matrix adhesion (34-36). Paradoxically, mucins also may promote cell adhesion. Selectin ligands are carried by mucin glycoproteins (37, 38); however, there is little evidence that selectin ligands occur or function physiologically at extravascular sites. Nonetheless, the presence of mucins does not necessarily imply non-adhesiveness, in all cases.

MUCIN EXPRESSION IN THE REPRODUCTIVE TRACT

Relatively little is known about mucin expression in the male reproductive tract. Among male reproductive tract tissues, the prostate has been studied most, in this regard. It is clear that both normal and malignant prostate epithelia display histologically detectable mucins (39); however, there is a shift from mucins bearing neutral oligosaccharides toward those bearing acidic oligosaccharides during conversion to a malignant state (40, 41). Among integral membrane mucins, MUC1 is highly expressed in the prostate (42, 43). Northern blot analyses failed to detect transcripts for the secreted mucins, MUC2 or MUC3, in either normal or malignant prostate (98), although antibodies directed against a peptide motif of the tandem repeat region of MUC2 did react with this tissue (44). It is possible that MUC2 is transported to the prostate or that a protein bearing a related epitope occurs in this tissue. A recently-discovered gene encoding a protein with multiple membrane-spanning domains and mucin-like regions, HE6, is highly expressed in the epididymis (45). Surprisingly, a few reports indicate that mucins (MUC8) are present on sperm (46). It is possible that a mucin coat on sperm might reduce sperm adhesion during its transit through the male and/or female reproductive tract; however, the exact functions of mucins on sperm are not clear.

Considerably more studies have been done on mucin expression in the female reproductive tract, including ovaries, oviduct or fallopian tube, uterus, cervix and vagina. The physiology and morphology as well as glycoprotein biosynthetic capacity of female reproductive tract tissues are strongly influenced by steroid hormones (47-50). In addition, different regions of the female reproductive tract respond distinctly to steroid hormones. Therefore, knowledge of mucin expression in one region of the female reproductive tract is not necessarily predictive of expression in another region. In the complex tissue of the uterus, two types of epithelia, i.e., lumenal and glandular, occur that also display regional distinctions. Thus, it is important to determine the stage of the estrous or menstrual cycle from which tissues are prepared and, in the case of the uterus, the type of epithelium examined. These factors are not always clearly defined in the reports that have appeared.

Zona pellucida glycoproteins are produced in the ovary and surround mature ova (51). Several types of studies

indicate that the oligosaccharides of these glycoproteins play key roles in sperm-egg recognition (51, 52). There is little information on other mucin glycoproteins expressed in the ovary. Mucin biosynthetic enzymes also are found in normal ovarian tissues (53). Thus, the ovary is capable of assembling mucin glycoproteins; however, it is less clear whether mucin core proteins other than those for *zona* glycoproteins are expressed in this tissue. Conflicting reports have appeared on MUC1 expression in normal human ovary, perhaps due to differential specificities of the monoclonal antibodies used in these studies (43, 54, 55). Little Muc1 expression has been observed in the mouse ovary using antibodies that recognize all forms of Muc1 retaining a cytoplasmic tail (J. Julian and D.D. Carson, unpublished observations). MUC2 does not appear to be expressed in the human ovary (54). In contrast, it is generally observed that MUC1 as well as mucin-associated carbohydrate motifs are markedly elevated in malignant human ovarian tissue and cell lines (43, 54-56).

Unlike the ovary, the oviduct does typically express mucin genes in a non-transformed state. Of the eight human mucin genes cloned the oviduct expresses only MUC1 in the epithelium (57). More recently, a secreted oviductal protein, that has mucin-like properties is proposed to represent a secretory-type mucin and has been tentatively designated as MUC9 (58). The sequences of this mucin-like protein, oviductin, in rodents and humans displays the amino acid tandem repeat motif common to mucins. However, this motif is extremely divergent in the sequence for the human protein and absent in large domestic species (59). Unlike other mucin genes, which are often expressed in several tissues, oviductin is exclusive to the oviductal epithelium (59). This large molecular weight glycoprotein is extensively O-substituted with approximately 50% or greater (depending on species) of the molecular mass contributed by carbohydrates (59). In all species thus far examined, oviductin has been found to be regulated by the ovarian steroid hormones. It is not known if either MUC1 or oviductin are regulated by steroidal hormones in humans. The functions of either of these mucin proteins within the oviduct is as yet unknown. Given that oviductin has been shown to interact with both the ovulated ova and sperm as it traverses the oviduct, it has been postulated that this secreted glycoprotein may play a role in oocyte fertilization (52). Recently, Lapensee *et al.* (58) have postulated that this protein may prevent ectopic pregnancy by covering epithelial cells. The same role is possible for MUC1, given that it exhibits anti-adhesive characteristics in vitro (29). Clearly, more investigation into the roles of both mucins within the oviduct is necessary to determine their physiological functions.

A number of studies have appeared on mucin expression in the uterus. In all species examined to date, Muc1 is highly expressed in the uterus. Curiously, not all human endometrial cell lines express MUC1 and may even display ectopic expression of airway mucins (60, 61). This raises concern over the validity of using such cell lines for studies of regulation of mucin expression. In many species, Muc1 is down regulated in the lumenal epithelium during the phase where embryo implantation normally occurs (48-50, 62). This has lead to the suggestion that Muc1 serves as a barrier to embryo attachment under most conditions (48). Rabbits also express very high levels of Muc1 during the receptive phase; however, Muc1 loss is restricted to the immediate site of embryo attachment suggesting that an antiadhesive function is conserved in this species (49). The hypothesis that Muc1 prevents embryo attachment is supported by the demonstration that RU486 both inhibits embryo implantation and restores high level Muc1 expression in mice (48). Furthermore, while attachment competent embryos fail to attach to polarized uterine epithelial cells *in vitro* (28), they do so with high efficiency if mucins are enzymatically removed or if Muc1 is genetically ablated (M. DeSouza *et al.*, submitted). Maintenance of mucins at the apical surface of lumenal uterine epithelial cells may provide protection from infection until the point at which the embryo is ready to attach. In fact, the uterus appears to be generically more susceptible to invasion during the "receptive" phase since transplanted tumor cells more effectively penetrate the endometrium at this time (63, 64).

The major class of glycoproteins synthesized and expressed at the apical surface of polarized uterine epithelia in wild type or Muc1 null mice is mucins (28, 65). Mucins also account for a major class of glycoproteins synthesized by polarized uterine epithelia of other species as well (66, 67). In contrast, mouse uterine epithelial cells cultured on tissue culture plastic primarily synthesize N-linked glycoproteins. Culture on matrigel-coated plastic is not sufficient to restore the normal pattern of predominantly mucin-type glycoprotein synthesis seen under polarizing conditions (66). Therefore, adoption of a polarized state appears to be an important factor for mucin expression by uterine epithelia; however, although the mechanism underlying this response is not clear. Synthesis of mucins and many other classes of glycoproteins are strongly regulated by steroid hormones in the uterus. These responses are manifest both at the level of core protein mRNA expression and the activities of various glycosyltransferases (47 and refs. within, 48).

Muc1 accounts for less than 10% of the total complement of mucin oligosaccharides in mouse uterine epithelia (65). A comprehensive survey of mucin gene expression (MUC1-MUC7) revealed that only MUC1 and, to a lesser extent, MUC6 are expressed in the human uterus (57). A recently identified respiratory tract mucin, MUC8, also has been detected in human endometrium, although the expression of this gene varied considerably

from patient to patient, perhaps due to differences in menstrual cycle phase (68). Sialomucin complex also is expressed in rat uteri, although it is not clear if this occurs in other species (69). Antibodies recognizing a mucin-like glycoprotein of undefined core protein structure (MAG) also react well with human endometrial glands with maximal reactivity during the receptive phase (70). It is not clear if the epitope recognized by MAG antibodies represent pure carbohydrate determinants found on many mucins, or peptide epitopes of known or novel mucin core proteins.

A number of studies have focused on MUC1 protein and mRNA expression using samples from women with well-defined cycle phases. These generally reveal that MUC1 levels increase during the mid-luteal (receptive) phase (71-73). Nonetheless, expression of MUC1 glycosylation variants decreases during the receptive phase (74). These studies primarily described expression in glandular epithelium, the major epithelial component of human uteri. Patterns of glandular and lumenal Muc1 expression are quite distinct in the baboon (62). More recently, studies have been performed on human endometrial samples in the mid-proliferative (non-receptive) and mid-luteal (receptive) phases with clearly defined lumenal epithelia (DeLoia *et al.,* submitted). These results support the notion that MUC1 expression is maintained throughout the epithelia in the receptive phase in humans; however, like the baboon, MUC1 shows regional specialization in terms of its pattern of expression. This specialization does not appear to occur at the level of MUC1 core protein expression, but rather at the level of carbohydrate modifications. Lumenal and glandular epithelium becomes more modified with keratan sulfate and sialic acid residues during the receptive phase (75, 76). Such modifications can mask certain MUC1 ectodomain epitopes (16, 77, 78) and may explain earlier, apparently conflicting, reports of MUC1 expression in women.

The function of the changes in MUC1 "glycoforms" at the uterine lumenal surface is not clear. Modification with keratan sulfate would be expected to further enhance antiadhesive function (79, 80), an undesirable property for an embryo attachment molecule. Presuming an antiadhesive function with regard to embryo attachment in humans, MUC1 would have to be locally removed at the site of embryo attachment as occurs in rabbits (49). An interesting counterproposal is that MUC1 may actually support embryo attachment. This proposal gains strength from observations that mucins can be selectin ligands (81) and the detection of sialyl-Lewis X and A oligosaccharides in epithelial cells in receptive phase uteri and on MUC1 expressed by human uterine epithelial cell lines (50). Furthermore, L-selectin is expressed at early stages of preimplantation development in the human embryo (82). Studies in mice indicate that other carbohydrate motifs (lacto-*N*-fucopentaose-I) potentially found on mucins also may support embryo attachment (83). Studies focusing on the expression of LNF-I and selectin ligands at the lumenal surface of human uterine epithelium as well as the expression of adhesion molecules on the surface of human blastocyst stage embryos will be required to resolve these issues.

In addition to MUC1, the human cervix also expresses several other mucins including MUC4, 5AC, 5B, MUC6 and MUC8 (57). In rabbits, Muc1 levels do not vary more than 2-3-fold in response to steroid hormones in marked contrast to the large (10-fold or greater) changes seen in the uterus (49, 50). Epithelia of both tissues express steroid hormone receptors and are strongly influenced by ovarian steroids. Therefore, this is a clear example of the tissue specificity of regulation of mucin expression. It is possible that steroid hormones modify the production of signals by underlying stroma that, in turn, regulate mucin production in the epithelium. Both MUC1 and MUC4 are expressed by human vaginal epithelium, although MUC4 expression is not observed in all cells of this tissue (57). Cycle (hormone)-dependent alterations in the production of cervical vaginal mucus is a well-described clinical phenomenon (84 and refs. within); however, it is not clear if the source of the mucins in vaginal fluids is the vaginal tissue itself or cells from tissues in the upper reproductive tract.

SUMMARY AND FUTURE DIRECTIONS

Reproductive tract mucins can perform a variety of functions that include lubrication and protection from enzymatic and microbial attack. Relatively little is known about the types of mucins in the male reproductive tract or how mucin expression varies in response to male hormones. Mucin expression has been better studied in the female reproductive tract. Some mucins are highly restricted in female reproductive tract tissues, e.g., MUC9 or oviductin, while others such as MUC1 appear to be present throughout many tissues. Moreover, MUC1 expression is regionally specific. In most species, uterine MUC1 expression changes dramatically in response to steroid hormones while in other reproductive tract mucosa MUC1 expression remains fairly constant. These observations suggest that MUC1 performs a different or unique function in the uterus than in other regions of the female reproduction tract. Maintenance of mucin expression in non-uterine tissues may afford protection from infection, a process that severely impairs reproductive success. Loss of MUC1 occurs during the time of embryo implantation in most species. Furthermore, *in vitro* studies indicate that mucins, in general, and MUC1, in particular, provide a barrier to embryo attachment. Strategies for MUC1 removal during the time of embryo attachment vary markedly among species. More work needs to be done to determine the precise mechanisms underlying

MUC1 and mucin removal in the uterus. Such information might provide new avenues toward improving success rates in assisted reproductive technologies in humans and animals. Moreover, additional cell biological and molecular genetic approaches should provide a better understanding of mucin function in the reproductive tract.

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