

MUCINS: POTENTIAL FOR OVARIAN CANCER BIOMARKERS

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Abstract

Mucins comprise a wide range of proteins which generally expresses at the cell surface, heavily glycosylated and functions as providing the protection to the cell membrane. It is now reported that aberrant form of mucins is generally related with the pathogenesis of a number of cancer, including ovarian cancer. This review is focuses on the role of mucin as potential biomarker for the ovarian cancer.

Keywords: Mucins, Ovarian cancer, Pathogenesis, Biomarker

1. Introduction

1.1 Mucins: The extracellular glycosylated

Proteins: Mucin are known to provide the protection to the epithelial tissues as they are large extracellular heavily glycosylated proteins¹⁻³. They are also reported to prevent the attachment to a variety of microorganisms, toxins, proteases, lipases, glycosidases. Few of the protein are shown to have taken part in the cell signaling events. Recently they are reported to have a profound effect on the cell proliferation and transcriptional activation of a number of genes⁴.

1.2 Types of mucins: Mucins are comprises a long family of twenty proteins which can be broadly classified in to two major categories: secreted mucins (gel forming: MUC2⁵, MUC5AC⁶, MUC5B⁷, MUC6⁸, and non-gel forming: MUC7⁹ MUC8¹⁰ and MUC11¹¹), and membrane bound mucins (MUC1¹², MUC3¹³, MUC4¹⁴, MUC9¹⁵, MUC10¹⁶, MUC12¹⁷, MUC13¹⁸, MUC16¹⁹, MUC17²⁰, MUC18²¹ and MUC20²²).

1.3 Functional significance of mucins

proteins: Mucins are known to play a diverse role in the body. They are generally associated with providing protection to the cells from a number of microorganisms. They are thickly glycosylated.

It appears that mucins have the capability of serving as cell surface receptors and sensors and conducting signals in response to external stimuli for a variety of cellular responses like cell proliferation, cell growth, differentiation and

apoptosis. All mucins share general characteristics. For example, they have repetitive domains of peptides rich in serine, threonine, and proline in their backbone. Serine and threonine are sites for O- and N-glycosylation. Presence of the tandem repeat domain which varies in number, length and O-glycosylation is the common structural feature of all mucins^{12, 23-24}. Their general structure and biochemical composition provides protection for the cell surface and specific molecular structures regulate the local microenvironment near the cell surface.

1.4 Ovarian cancer and aberrant expression of mucins:

The mucins expression is pertained to the ovarian surface epithelium. Among all the mucins, MUC1 is well studied and reported to be expressed at the detectable level from ovarian surface epithelium²⁵⁻²⁶. Accumulating report has suggested that in comparison to benign and borderline ovarian tumors, malignant ovarian tumors are shown to have high expression of the mucin proteins. These are including the overexpression of the MUC1, MUC2, MUC3, MUC4, MUC5AC and MUC16 or CA125^{26, 27-31}. Giuntoli et al (1998) have employed the northern blot studies and reported that the MUC3 and MUC4 are expressed at very high level in the early stage of the ovarian cancers in comparison to the late stage ovarian tumor sample. They also stated that mucins high expression is playing a significant role in the protective function of the ovarian cancer. Similar result was also reported in various studies performed on the patient

samples³²⁻³⁴. Chauhan *et al* (2006) has identified a novel membrane anchored form of mucin, MUC13 in ovarian cancer. These studies have strongly suggested the role of the aberrant mucin expression is related with the progression of the ovarian cancers. These proteins may also have implicated in a number of other processes including exfoliation, dissemination, and invasion of the cancer. Once they are aberrantly glycosylated they lead to a protrubance of 200-2000 nm on the cell surface³⁵⁻³⁷. In the process of metastasis, ovarian cancer detach from the adjacent cells and it has been reported that mucin once becomes aberrant lead to abolishing the cell-cell contact detachment, which further allowing the cell to traverse the basement membrane and migrate through stroma to reach the blood vessels or the lymphatic systems³. There are few studies which are reporting the role of mucins in the immunosuppression^{3, 35-40}. In their structure there are a 2-3 EGF like domain are there and it is reported that they have pivotal role in the cell proliferation by elucidating the intercellular signaling events⁴⁰⁻⁴⁴. The role of MUC16/CA125 in ovarian cancer metastasis has been shown in the recent studies. It shows high affinity interaction with the mesothelin (glycosylphosphatidylinositol anchored glycoprotein) facilitating the peritoneal metastasis of ovarian cancer cells⁴⁵⁻⁴⁶. Additionally, the expression of MUC16/CA125 has been shown to down regulate the activity of CD16 in ovarian cancer cells and inhibition of cytotoxic responses of human natural killer (NK) cells. It has also shown selective binding to CD16+ NK cells in ovarian cancer patients up to 30 -40%. These studies advocate the immunosuppressive properties of MUC16/CA125⁴⁷. It is suggested that expression of mucin can alter the cellular characteristics of ovarian cancer and results revealed the peculiar role of mucins in ovarian cancer and its involvement in the pathogenesis of ovarian cancer.

1.5 Mucins: Potential ovarian cancer biomarker: The expressions of mucins are generally confined to epithelial surfaces and exposed to circulation. The potential of mucins as serum markers of various tumors especially ovary has already been established their overexpression may establish them as potential biomarkers for other tumors or diseased conditions. The diagnostic character for the detection and monitoring of cancer has been provided by O-glycosylation of mucins which is prominent in epithelial cancers. In the malignant

conditions O-glycosylated mucins enter the bloodstream.

MUC16 is heavily glycosylated, large and transmembrane mucin. The importance of CA125/MUC16 in the diagnosis of ovarian cancer has been shown in several studies. Even the preferred non-invasive test for the diagnosis of ovarian cancer is the increased level of CA125/MUC16. In addition, the antigens, present on these mucins, such as CA19-9, CA50, and CA242 are also recognized as the serum markers of different diseased conditions. Moreover, a potent antibody response can be elicited by the expression of mucins as it may possibly be immunogenic. The response of antibody may act as an indicator of a disease.

It has been demonstrated in a recent study of blood plasma samples the presence of antibodies of MUC1 was inversely correlated with risk of ovarian cancer. These studies supports that mucin expression has potential to serve as biomarker of ovarian cancer and its prognosis.

2. Therapeutic approaches targeting the mucins

In the recent years projects related to the development of tumor vaccines have received extensive attention thus currently the development of the cancer vaccines is the focus of research. In a cell based vaccine approach the tumor cells are derived from the same patient (autologous) or a different patient (allogeneic) or dendritic cells (activated by antigen of cancer). These vaccines are administered to stimulate the immune system of a cancer patient. The tumors in which mucin antigens are overexpressed may be targeted by inducing the potential anti-MUC responses. MUC1 has been used as a marker in the progression of a disease and in immunodirected therapies as a successful target. For vaccination studies the use of naked DNA is another simple and attractive approach.

MUC1 cDNA has been shown its potential in long-term growth suppression of tumors as a cancer vaccine in mouse models. A potent cytotoxic T-cell response has been induced and therapeutic benefits has been provided by the dendritic cells pulsed with peptides derived from mucins. It may be a potential approach for the treatment of ovarian tumors known for mucins overexpression with a better outcome of survival.

3. Conclusions

As discussed the role of various mucin in the ovarian cancers. And all these are pointing

towards the potential role of the mucins in the diagnosis and treatment of the malignancy. However more efforts are required to address the molecular mechanisms.

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