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Review

Mucins in the pathogenesis of breast cancer: Implications in diagnosis, prognosis and therapy

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ABSTRACT

Mucins are high molecular weight, multifunctional glycoproteins comprised of two structural classes—the large transmembrane mucins and the gel-forming or secreted mucins. The primary function of mucins is to protect and lubricate the luminal surfaces of epithelium-lined ducts in the human body. Recent studies have identified a differential expression of both membrane bound (MUC1, MUC4 and MUC16) and secreted mucins (MUC2, MUC5AC, MUC5B and MUC6) in breast cancer tissues when compared with the non-neoplastic breast tissues. Functional studies have also uncovered many unique roles of mucins during the progression of breast cancer, which include modulation in proliferative, invasive and metastatic potential of tumor cells. Mucins function through many unique domains that can form complex association with various signaling molecules including growth factor receptors and intercellular adhesion molecules. While there is growing information about mucins in various malignancies including breast cancer, no focused review is there on the expression and functional roles of mucins in breast cancer. In this present review, we have discussed the differential expression and functional roles of mucins in breast cancer. The potential of mucins as diagnostic and prognostic markers and as therapeutic targets in breast cancer have also been discussed.

Contents

Abbreviations: BC, breast cancer; UEH, usual epithelial hyperplasia (also called ductal hyperplasia DH); ADH, atypical ductal hyperplasia; CIS, carcinoma *in situ*; SRCC, signet ring cell carcinoma; FGF, fibroblast growth factor; EGFR, epidermal growth factor receptor (also called ErbB1); MUC1, cytoplasmic tail (MUC1-CT); EGF, epidermal growth factor; PTD, Protein transduction domains; MTS, membrane translocating sequences; MCA, mucin-like carcinoma associated antigen

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1. Introduction

Breast cancer (BC) is the second leading cause of cancer-related deaths in women worldwide after lung cancer. In the year 2010, BC accounted for an estimated 28% of all new cancer cases in the United States, while nearly 15% deaths from this malignancy occurred in the same period [1]. While most BCs are sporadic in nature, approximately, 5% of BC patients have a hereditary predisposition to develop this malignancy. Evidences are emerging those suggest that BC is a heterogeneous disease at the molecular level having a number of distinct entities with specific pathologic features and biologic behaviors [2]. Traditional grading systems based on the characteristics of the nucleus have given a way to more molecular approach that relies on distinct gene signatures to separate the different BC subtypes. The molecular classification of BC have been studied by several groups of investigators [3–9]. These approaches are an attempt to avoid over- or under-treatment and personalized therapy based on the predicted behavior of a given subtype.

Molecular markers are particularly helpful as an alternative to conventional diagnostic modalities as expression of mucins generally precedes morphological change by a considerable lag period. According to the currently available information, the development of BC represents a continuum of events and is believed to progress from non-neoplastic epithelium through the stages of usual epithelial hyperplasia (UEH also called ductal hyperplasia DH), atypical ductal hyperplasia (ADH), carcinoma *in situ* (CIS) and finally invasive carcinoma. Molecular studies seem to support the hypothesis that the transition between UEH and ADH represents the boundary between benign hyperplasia and CIS (the stage preceding invasive carcinoma) [10]. Molecular markers that can distinguish these two lesions could thus have the potential to be immensely useful to identify patients at an elevated risk for BC and therefore requiring enhanced surveillance.

The overexpression, mutation, and deletion of specific genes are major mechanisms underlying the progression and metastasis of BC. Mucins (denoted by the gene symbol MUC) encompass a family of high molecular weight, heavily O-glycosylated proteins that are differentially expressed in several epithelial malignancies [11–14]. These proteins have been demonstrated to play a pivotal role in the development of BC. Mucins are normally expressed by epithelial cells and contribute to the lubrication of hollow tubular surfaces such as ducts and the passages in the respiratory and gastrointestinal systems. They also serve as a mechanical barrier to extrinsic physical and biological assaults [15,16]. Mucins are broadly classified structurally into two main classes: membrane-bound mucins (MUC1, MUC3A, MUC3B, MUC4, MUC12, MUC13, MUC15, MUC16, MUC17, and MUC20) and secreted or gel-forming mucins (MUC2, MUC5AC, MUC5B, MUC6, MUC7, MUC8 and MUC19) [11,14,15,17]. All mucins share certain common structural features, but are distinct in the sequence, domain organization, length, and number of their respective tandem repeat sequences [18]. The structure and general biology of mucins have been reviewed in several excellent review articles [13,15,16,19,20].

An altered expression of mucins has been reported to be associated with cancer progression, which in turn, influences cellular growth, differentiation, transformation, adhesion, invasion, and immune surveillance. Mucin 1 (MUC1) is the mostly-studied mucin in BC. However, recent studies have demonstrated that other mucins, including MUC2, MUC3, MUC4, MUC5AC, MUC5B, MUC6, and MUC7, are also differentially expressed in BC cells. In this present review, we have discussed the current knowledge concerning the expression, clinical relevance and functional role of mucins in BC. Investigation by several research groups has revealed that mucins have important roles in the pathological state and have immense potential as diagnostic or prognostic markers and as therapeutic targets in BC.

2. Expression of mucins in the normal breast and their aberrant expression in benign and malignant breast diseases

2.1. Expression of mucins in the normal breast

Several mucins have been reported to be expressed by the non-neo-plastic breast (summarized in Fig. 1 and Table 1). MUC1, the best studied mucin in BC, is expressed in nearly 59% of normal breast tissues (without an adjoining malignancy) with a similar degree of positivity in the malignant ducts adjacent to the normal tissue [21]. MUC4 (92–100% positivity in a single study [22] and to a lesser extent MUC5AC (4% positivity [21]) and MUC6 (9–14% positivity [21,23]) are also expressed in the ductal epithelium of the healthy breast. MUC2 expression is however entirely absent. MUC5B, while not expressed in the non-neoplastic ductal epithelium, was detected in cancer adjacent normal tissues (42% positive cases in one study) [24]. At the subcellular level, MUC1, MUC5AC and MUC6 are expressed mostly in the cytoplasm [21,25], while MUC5B is expressed in the apical portion of the non-neoplastic ductal cells of the breast [24].

2.2. Expression of mucins in benign and potentially malignant breast diseases

Present models of BC development suggest that it develops through the stages of hyperplasia (two types—usual and atypical), carcinoma *in situ* and invasive adenocarcinoma. However, while every carcinoma develops from a carcinoma *in situ*, not every carcinoma *in situ* develops into a carcinoma. Molecular markers are thus particularly helpful as an alternative to conventional diagnostic modalities to identify potentially malignant lesions as their expression precedes morphological changes by a considerable lag period. Several studies have demonstrated that the expression of mucins is altered in benign and pre or potentially malignant breast diseases (Table 3 and Table 4). For instance, the expression of the membrane mucin MUC5B is upregulated in fibroadenomas, a fibrocystic disease of the breast and in sclerosing papillomas [24]. MUC6, on the other hand, is expressed in fibrocystic disease without atypia, and its expression increases in cases with accompanying atypical features (41% positivity in cases without atypia vs. 100% in those with atypia) [23]. MUC1, MUC2, MUC5AC, MUC5B, and MUC6 are also expressed in pre-malignant breast lesions like ductal carcinoma *in situ* (DCIS), while MUC2 expression is upregulated in lobular carcinoma *in situ* (LCIS), the precursor to invasive lobular carcinoma [21,24,26]. MUC1 and MUC6 (but not MUC5AC) are also expressed in simple ductal hyperplasia without atypia [21]. A case report noted that there was positive staining for MUC1 (92–100% positive cells) but not for MUC2 or MUC5AC in two cases of ductal adenoma of the breast. Weak MUC6 positivity (5% positive cells) was also seen in one case in the same study, while the other was entirely negative [27].

Using monoclonal antibodies that recognize epitopes in either the tandem repeat (TR) region (C595, HMFG2 and SM3) or the cytoplasmic tail (CT33) of MUC1, it was observed that normal breast ductal epithelium was variably immunopositive (range: 8–92%). Majority (>70%) of the normal breast tissue sections exhibited an apical, predominantly linear MUC1 staining with the remaining cases showing a non-apical cytoplasmic staining. MUC1 positivity, particularly with the CT33 antibody, was maintained in a range of benign (fibroadenoma, non-proliferative lesions, usual epithelial hyperplasia) and pre-malignant lesions (atypical hyperplasia). The incidence of MUC1 immunopositivity, however, was significantly lower with the SM3 anti-TR antibody (ranging from 4% to 14%) compared to the other two TR antibodies, HMFG2 (36–65%) and C595 (44–61%). Significantly, the highest reactivity (between 71% and 96%) was noted with the antibody directed against the MUC1 cytoplasmic tail (MUC1-CT) in both normal breast tissues and those from patients with benign breast diseases [28]. These differences in reactivity to MUC1 antibodies are suggested to be a