Medical Hypotheses 84 (2015) 413–416

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Role of tumor-associated glycoprotein-72 in the progression of endometrial adenocarcinoma: A proposed study

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ARTICLE INFO

Article history:
Received 18 June 2014
Accepted 21 October 2014

ABSTRACT

Endometrial adenocarcinoma is on the basis of the molecular, immunohistological and clinicopathologic features broadly divided into two groups, referred as type I and type II. Type I appears more frequently and in principle patients have a good prognosis; however a significant number of patients develop local recurrences. We hypothesize that TAG-72, expressed on endometrial carcinoma binds and internalizes endocytic pattern recognition receptors on surrounding tissue antigen presenting cells (dendritic cells and macrophages), powers their anti-inflammatory maturation program and make them capable to elicit or modulated tolerogenic immune response mediated by local T and NK effectors. This could support uncontrolled local tumor growth, deeper tumor invasion into surrounding tissues, frequent local recurrences and/or lymph node metastasis. To test this hypothesis, we propose a semi-quantitative immunohistochemical analysis of TAG-72 expression in endometrial adenocarcinoma samples and to correlate the results with clinical and pathological parameters (age, type and histological grade of the tumor, estrogen and progesterone receptor expression, invasion into the myometrium and capillaries, presence of lymph node metastases, FIGO stage, and TNM classification). It would be worthwhile to investigate the local tissue immune response in the tumor environment using tissue samples removed during surgery. These studies could elucidate the underlying immunopathological mechanisms that govern the early recurrence and possibly distant metastases of TAG-72-expressing adenocarcinomas and might help in deciding the type of treatment to be applied in a selected group of cancer patients including application of biological therapy with anti-TAG-72 antibodies, according the principle of personalized oncology treatments.

Introduction

Endometrial adenocarcinoma is the most common gynecological malignancy in developed countries [1]. The incidence rate differed significantly between developed countries with higher incidence and undeveloped countries with lower incidence rates [1]. On the basis of the molecular, immunohistological and clinicopathologic features endometrial carcinoma is broadly divided into two groups, referred as type I and type II. Type I endometrial carcinoma begins as simple endometrial hyperplasia, which progresses to complex atypical hyperplasia, which develops into the precursor lesion and finally in endometrial intraepithelial carcinoma [2]. These processes are accompanied with unopposed estrogenic stimulation in pre- and perimenopausal women and they are associated with the mutation of K-ras and tumor suppressor phosphatase and tensin homolog gene. Type I carcinomas are the cancers of low tumor grade, often with indolent behavior and slow penetration in the lymph node, as it was proven for the most common subtype named endometrioid adenocarcinoma [2]. However, they show microsatellite instability, local invasion and frequent recurrences, requiring frequent medical examinations and modification of anticancer therapy. Endometrial carcinomas type

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http://dx.doi.org/10.1016/j.mehy.2014.10.017
0306-9877/

II represents the minor part (10–20%) of women with endometrial malignancy and include uterine serous and clear-cell carcinoma [3]. Both subtypes appear to progress from an atrophic endometrium to the precursor lesion and endometrial glandular dysplasia in postmenopausal women with the mutation of tumor suppressor gene P53 [2]. Serous endometrial carcinoma is aggressive tumor that extensively penetrates the lymph and blood vessels; even if they are limited to the endometrium or endometrial polyps [4,5]. Their stage-adjusted 5-year overall survival rate has significantly worse prognosis compared to type I carcinomas [5].

Increased production of highly glycosylated proteins (mucins) during differentiation of the endometrial carcinomas is recently considered as an independent risk factor for their spreading to the regional lymph nodes [6]. However, Schwartz et al. reported that TAG-72 expression, using the antibody of B72.3 clone was not common in hyperplastic endometrium and were not associated with clinical progression of hyperplasia in endometrial adenocarcinoma [7]. Possibly due to concomitant unopposed estrogenic stimulation, as estrogen could play an inhibitory role on the expression of TAG-72, while progesterone had no direct effect [8]. Accordingly, TAG-72 has never been identified in endometrium during the proliferative phase, which is characterized by estrogen domination [9]. However, TAG-72 was detected in premalignant colon lesions [10], probably due to the intrinsic characteristic of colon tissue, which are sex steroids independent. Paracrine/autocrine mechanisms are likely to be involved in the local regulation of TAG-72, since its expression has been strictly temporally and spatially distributed [8,10]. TAG-72 is oncofetal antigen, and it is present in gonadal tissues of both sexes from 13 to 34 weeks of gestation, as well as in the epithelium of the digestive tract, respiratory tract, transitional epithelium of the kidney and Hassall's corpuscles in the thymus early during gestation [11]. It is also present in mammary, salivary and prostate glands [12]. Nearly two decades ago, TAG-72 was detected in the glandular epithelium of functional zone in the uterine fundus during the secretory phase of cycling endometrium [9]. During the secretory phase TAG-72 was also found in the mucous endometrial secretions, but TAG-72^{+} cells were rare in the lower uterine segment [9].

TAG-72 expression in normal cycling endometrium occurs simultaneously with the accumulation of immune cells in the secretory phase [13,14]. In immunohistochemical study of leucocyte subpopulations on biopsy specimens of human endometrium revealed that the most prominent population are macrophages [15]. Beside macrophages, endometrium and early pregnancy decidua contain tiny, population of dendritic cells, mostly of myeloid origin [16], as another subset of professional antigen presenting cells. They initiate immune response after the interaction with antigens and orientate the action of immune effectors toward pro-inflammatory immune response or anti-inflammatory tolerogenic reaction. TAG-72 seems to be natural ligand for the pattern recognition mannose receptor and dendritic cell specific ICAM non-integrin (DC-SIGN), expressed on early decidual dendritic cells [17,18] and macrophages [12,19], as well as tumor associated macrophages [20]. After stimulation with TAG-72, decidual dendritic cells enhanced CD83 expression, but decreased intracellular expression of pro-inflammatory cytokines interleukin (IL)-15 and interferon gamma, when compared to untreated cells [17], indicating that TAG-72 induced their anti-inflammatory and tolerogenic maturation program. It is confirmed with the fact that a strong inducer of a Th1 type response, lipopolysaccharide, failed to increase pro-inflammatory interferon-gamma production in TAG-72 pretreated CD1a^{+} dendritic cells [17]. In a similar manner, tumoral mucins, including TAG-72 increase of IL-10, inhibit IL-12, and decrease the Th1-attracting chemokine CCL3 secretion by tumor associated macrophages [20], suggesting their tolerogenic properties.

Interaction of tissue conditioned and alternatively activated, dendritic cells and/or macrophages with surrounding cognate T and NK cells is of particular importance for the orchestration of local immune response [16,18]. *In vitro*, decidual T cells proliferated less efficiently and decreased interferon-gamma expression, after the close contact with TAG-72 treated decidual CD1a^{+} DCs, when compared with untreated cells [17]. It suggests *in vitro* anti-inflammatory orientation of T cells, in the presence of TAG-72. The same mechanism possibly acts in secretory phase endometrial tissue. Indeed, T lymphocytes were present in a relatively small number in the endometrium [15], including their subsets gamma/delta T cell receptor positive cells, T regulatory cells and NKT cells [21]. The frequency of cytotoxic CD8^{+} T cells and regulatory T cells were higher in complex atypical hyperplasia and well-differentiated endometrial carcinoma before, then after the therapeutic progestin administration [22]. Treatment with progestin increased NK cells in the surrounding of endometrial carcinoma [22]. It could be due to the recruitment of peripheral blood NK cells in the tumor surrounding. Under the influence of progesterone, glycoproteins expressed on endometrial endothelial cells, are involved in rolling of peripheral blood CD16–NK cells on microvascular endothelium [23], which enable recruitment of peripheral blood NK cells in the secretory phase endometrium and the decidua of normal early pregnancy, where they proliferate under the influence of IL-15 and finish development in specific uterine microenvironment [23,24]. NK cells of unique CD3–CD16–CD56 $^{bright+}$ phenotype and function prevail among leukocytes in early pregnancy decidua [14,25]. They are abundantly equipped with cytotoxic mediators, perforin and granulysin in pregnant and non-pregnant uterus [25], and they are thought to be essential effector cells in response to different foreign and/or own threats, acting without previous stimulation [12]. However, NK cytotoxic activity is strictly regulated by local microenvironmental factors, including the interactions with surrounding antigen presenting cells (macrophages and dendritic cells) [26,27] and many soluble mediators [12]. We showed previously that mucin 1 pretreated decidual macrophages, were able to elicit tolerogenic functional properties of decidual NK cells by restricting their proliferation rate and expression of cytotoxic mediators [27], but there have not been reports of the interaction of TAG-72 conditioned decidual dendritic cells and cognate decidual NK cells, which could affect anti-tumor immunity. Namely, anti-tumor immune response is an additional predictor of survival in well-differentiated endometrial carcinoma [22]. In spite of continuous research of glycoprotein biology, it is not quantified yet TAG-72 expression in various type of endometrial carcinoma and it is not correlated TAG-72's surface expression or secretion into extracellular space with the immune control of endometrial cancers, their microsatellite formation, local invasion, frequent recurrences and/or nodal metastasis [6,10,28,29].

Hypothesis

Our hypothesis is that TAG-72, expressed in endometrial carcinomas cells and/or secreted in the extracellular space, binds and internalizes endocytic receptors in surrounding tissue antigen presenting cells, supports their maturation program capable to elicit anti-inflammatory and tolerogenic local immune response mediated by T and NK effectors. Tumor-associated DCs and macrophages conditioned with TAG-72 are likely inefficient at facilitating a Th1-mediated response [20]. It might help tumor cells to avoid immune reactivity and induce deeper penetration of malignant cells into surrounding tissue, and frequent local recurrences of endometrial carcinoma type I, regardless of the degree of tumor differentiation. The poorer prognosis associated with mucinous endometrial cancers supports this hypothesis [6].