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REVIEW ARTICLE

Adhesion molecules in cancer of the head and neck: role of dysadherin

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Summary

Dysadherin is a recently discovered cancer-related cell membrane glycoprotein that has an important role in tumor progression and metastasis. We are focusing on the role of dysadherin in E-cadherin downregulation, the different expression patterns of the molecule in cancer of the head and neck and its potential role as a molecular target for future applications in diagnosis, prognosis, and management of the disease.

Key words: adhesion molecules, dysadherin, E-cadherin, head and neck cancer

Introduction

Adhesion molecules are known to play a central role in cell-cell interactions and interactions between the cell and the surrounding environment. Current research assigns great importance to the participation of the E-cadherin-mediated adhesion system in tumor progression and metastasis in various types of cancer [1-3]. E-cadherin, or uvomorulin, is the classical type I cadherin and is an integral membrane glucoprotein with a single transmembrane domain. Mostly present in cells of epithelial origin, it is localized to specialized junctions of the zonula adherens type where it is known to organize the various junctional components by activating protein kinase C [4].

E-cadherin interacts in a homophilic manner (E-cadherin binds to E-cadherin) linking subsequently by its cytoplasmic domain to the intracellular undercoat proteins beta-catenins [5,6]. The protein alpha-catenin attaches the microfilaments and the cytoskeleton-associated proteins to the beta-catenin- E-cadherin complex. The interaction of the above proteins results in a dynamic physical connection which plays also a functional role in cell signaling. During the last decade, germline E-cadherin gene (CDH1) mutations were found to predispose to familial cancers of the gastrointestinal tract [7] while downregulation of E-cadherin expression has been associated with poorly differentiated carcinomas and underexpression of E-cadherin seems to have prognostic significance for the clinical outcome in many tumor types.

The downregulation in the expression of E-cadherin therefore, has been strongly associated with reduced intercellular adhesiveness. The loss of normal adhesive function of the cells is a standard characteristic of malignant tumors, associated to their invasive and metastatic properties.

Dysadherin is a recently characterized and cloned cell membrane glucoprotein. The cDNA for the antigen encodes 178 amino acids, which include a putative signal sequence, a potential O-glycosylated extracellular domain, a single transmembrane domain, and a short cytoplasmic tail [8]. Recent evidence suggests that dysadherin has an important role in the downregulation of E-cadherin protein functioning as an "anti-adhesion" molecule. This downregulation seems to occur in a post-transcriptional level without affecting the mRNA levels of the protein. The discovery of this transmembrane regulator of the E-cadherin adhesion system that could play the role of biological prognostic marker highlights the need for further study, particularly in tumors of epithelial origin where the above-mentioned system is of major importance.

Expression of dysadherin in normal tissues and in cancer of the head and neck and the regulatory role for E- cadherin expression

Malignancies of the head and neck refer to tumors

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of the upper aerodigestive tract, the salivary glands, the thyroid and parathyroid glands, the sino-nasal tract and the skin of the head and neck. The majority of these tumors (>90%) are squamous cell carcinomas ranging from poorly to well differentiated. Head and neck squamous cell carcinoma (HNSCC) is one of the most common cancers worldwide with a higher incidence in certain countries, mostly in south Asia. The median age at presentation is 60 years. However, the incidence of these cancers in young adults (< 40 years) appears to be increasing [9]. This epidemiological phenomenon and the fact that head and neck cancer has disastrous biologic effects, serious psychological consequences in the patient, emotional cost in his family and social environment and also economic impact in public health, have established this malignancy as one of the most challenging therapeutic targets. The therapeutic problem of head and neck cancer becomes more intense as it appears that there is not essential improvement in survival during the last decades, despite the progress in surgical, radiological and chemotherapeutic modalities [10]. There is a strenuous effort worldwide today to identify new methods to estimate basic prognostic factors of the disease, mainly in the molecular level, and correlate these factors with possible therapeutic strategies [11-13]. In parallel, recent advances in molecular biology have documented the role of genetic alterations in tumorigenesis and have led to the development of potential new therapeutic approaches designed to target the mutated gene or genes that contributed to malignant transformation or that are contributing to tumor progression and metastases [14]. Integrins have been used as research targets toward these directions since their role in cancer and metastasis is established and well reviewed in bibliography [15-17] and the derangement in their expressional patterns seems to coexist with a number of aberrant cellular activities during tumor development, progression and metastatic dissemination [16,17]. Some other molecular markers have also been used to derive prognostic information about HNSCC, including epidermal growth factor receptor (EGFR) [18], transforming growth factor alpha [19], cyclin D1 [20], and cytokeratins [13].

Dysadherin is known to be expressed mainly in malignancies of the stomach, colon, pancreas and breast [8]. In contrast, it is found only in a limited number of normal tissues; it has been demonstrated that dysadherin is expressed mainly in epithelial tissue such as kidney, intestine, and lung. In kidney, the expression level appears to be highest in the cortex with reduced labeling in the medulla and papilla. In the intestine it is present mainly in the duodenum [21]. Normal lymphocytes, endothelial cells and basal cells of stratified squamous epithelia have shown dysadherin expression as well [8]. In HNSCC, dysadherin immunostaining is observed in the membranes of the cancer cells, mainly in the intercellular borders of cancer cells and in poorly differentiated tumors [22,23]. In the above mentioned studies, the presence of dysadherin in lymphocytes and endothelial cells was confirmed whereas the expression of the protein in the basal cells of normal stratified epithelium was used as a positive control for these squamous-origin tumors. Immunoreactivity for dysadherin is completely absent from normal thyroid follicular epithelial cells and in specimens from thyroid gland tumors diagnosed pathologically as follicular carcinoma [24]. Papillary thyroid carcinoma, undifferentiated carcinoma of the thyroid and cutaneous melanoma commonly arising in the head and neck region have been found to exhibit strong immunoreactivity for dysadherin as well [24,25]. In all these studies where immunostaining methods were used to estimate the expression of the molecule, the cutoff point between positivity and negativity has been taken arbitrarily making the co-estimation of these results more complicated.

E-cadherin is considered to be the prime regulator of intercellular adhesiveness in epithelial cells [26]. Reduced expression of E-cadherin was associated with invasion, metastasis and ominous prognosis in a variety of epithelial malignant tumors [27,28] including HNSCC [29-33]. Ino et al. screened the expression of dysadherin and E-cadherin in more than 30 cell lines by Western and Northern blotting, demonstrating that dysadherin gene transfection in the above cells induced decreased expression and function of E-cadherin by a post-transcriptional mechanism [8]. An overt glycosylation of the dysadherin molecule in cancer cells seems to have a close relation to this phenomenon as we know that the O-linked glycosylation is necessary for stable expression of dysadherin and suppression of E-cadherin [34]. In the majority of the existing studies in the head and neck, the increased dysadherin expression appears to correlate with statistical significance with the E-cadherin downregulation confirming the above hypothesis. In melanoma, dysadherin was detected in parts of the tumor where E-cadherin was downregulated, leading the authors to suggest that there may be a threshold level of dysadherin expression beyond which down-regulation of E-cadherin ensues and that downregulation of E-cadherin expression is not the only mechanism by which dysadherin affects the aggressiveness of cutaneous malignant melanoma [25].

Dysadherin in the prognosis of head and neck cancer

Existing studies show that dysadherin expression appears to be an independent prognostic factor in various

Table 1. Dysadherin immunostaining in head and neck cancer; summary of the main existing studies in the literature. We used the cutoff of 50% to distinguish positivity and negativity of staining. It has to be noted that some authors subdivide the negatively stained specimens in low (< 20% positive cells) and intermediate (21-50% positive cells) categories [22-24]

Head and neck anatomic site	*Histologic type*	*Size of cohort*	*Immunostaining: Dysadherin positive in > 50% of tumor cells*	*Immunostaining: Dysadherin negative in > 50% of tumor cells*
Oral cavity and tongue	Squamous	114	81	33
Lower lip	Squamous	50	22	28
Larynx	Squamous	35	18	17
Thyroid	Papillary with undifferentiated carcinoma	21	4	17
	Papillary without undifferentiated carcinoma	30	0	30
	Follicular	10	0	10
	Undifferentiated	31	19	12
HNSCC	Squamous	199	121	78

HNSCC: head & neck squamous cell carcinoma

types of cancers, including cancer of the head and neck. Table 1 summarises the results of various studies regarding the anatomic region of the head and neck. Most of these studies use immunostaining methods to estimate the expression of the molecule in the tissues under study and the difference between the arbitrary limits of positivity and negativity of staining may make coestimation of results problematic. Prognostic indicators for head and neck cancer consist a field of intense study as prognosis remains stable during the last decades, despite the progress of technical means and the better understanding of the molecular background of the disease. Positive prognostic significance in dysadherin downregulation has been demonstrated in colorectal cancer [35], in pancreatic adenocarcinoma [36] and in the non-small cell lung cancer [37]. In a study of ours containing specimens from HNSCC, a clear positive correlation between increased dysadherin expression and negative prognosis was demonstrated [22]. In tongue cancer specimens, patients with dysadherin immunoreactivity in >50% of tumor cells survived a significantly shorter time than those with dysadherin immunoreactivity in < 50% of tumor cells [23]. In thyroid cancer dysadherin expression was significantly higher in patients who died from thyroid carcinoma than in the survivors [24]. Dysadherin seems to be frequently overexpressed in head and neck cancer and a possible role of the molecule as a reliable independent prognostic factor comes into sight, supporting future research efforts toward this direction.

Conclusion and future considerations

Head and neck cancer is a field of medicine where the demand for new molecular targets of diagnostic, prognostic and therapeutic significance is excessive and urgent. Dysadherin is a recently discovered molecule that seems to have a significant contribution in tumor progression and metastasis and its overexpression may reliably indicate the prognostic tendencies of the disease. Although the first studies are very encouraging, many factors have to be taken under consideration in the prospective use of the molecule for diagnostic and prognostic purposes. Dysadherin seems to be expressed in a variety of normal tissues, including lymphocytes and endothelial cells and may have an important role in regulating ionic exchanges in the human kidney or other essential normal cell functions that remain unknown. Still, it is under question how exactly it downregulates E-cadherin in the molecular level and whether it affects other transmembranic targets leading to parallel activation of other molecular pathways. Further elucidation of the functions and the regulatory role of dysadherin is necessary to estimate the potential implementation of this emerging knowledge in the demanding field of clinical diagnostic routine and therapeutics of head and neck cancer.

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