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THE ROLE OF INTERCELLULAR ADHESION MOLECULE-1 IN HEAD AND NECK CANCER

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The intercellular adhesion molecule-1 (ICAM-1) is a member of the immunoglobulin gene superfamily of adhesion molecules expressed in multiple human tissues and participating in various physiologic and pathophysiologic processes of the human body. The alterations in the expression of ICAM-1 in the various types of the cancer of the head and neck are discussed in this mini-review following the existing status from the current literature. Possible applications of this developing knowledge in the diagnosis and prognosis of head and neck cancer are briefly mentioned.
Key Words: **adhesion molecules, intercellular adhesion molecule-1, ICAM-1, oral cancer, head neck cancer.**

The interactions either among cells or among cells and components of the extracellular matrix are very important in the maintenance of epithelial cells structure and control of cell growth and differentiation. They are mediated by adhesion molecules which are involved in the processes of embryogenesis, morphogenesis, normal growth and development, leukocyte extravasation, blood coagulation, wound healing, in signal transduction as well as inflammation, cancer invasion and metastasis [1, 2]. Class of adhesion molecules comprises the major families: cadherins, integrins, immunoglobulin gene superfamily, selectins and CD44 [3–5]. The intercellular adhesion molecule-1 (ICAM-1) is a member of the immunoglobulin gene superfamily of adhesion molecules mainly expressed in leukocytes [6], endothelial cells [7], in certain types of epithelial cells [8] and fibroblasts [9]. ICAM-1 possesses five extracellular Ig-like domains, one transmembrane segment and a short cytoplasmic tail as presented in Figure [10]. Human ICAM-1 has five extracellular Ig-like domains [6–10]. Each of these domains presents different ligand specifity; for example the lymphocyte function associated antigen-1 (LFA-1) antigen is found to prefer the first Ig domain [11], whereas the Mac-1 binds to the third domain of the extracellular part of the molecule. The first Ig domain also harbours the binding site for major group human rhinoviruses (HRV) and *P. falciparum*-infected erythrocytes.

ICAM-1 IN HEAD AND NECK CANCER

The variable binding ability of the ICAM-1 is directly related to the multifunctional physiologic and biologic role of this molecule. The participation of ICAM-1 in inflammatory processes and in migration of activated leukocytes in inflammatory foci was first studied in the skin [12, 13] and is today well established. This is a complex process mediated by several adhesive molecules expressed both on the leukocyte and endothelial membrane. ICAM-1 is also known as a potent costimulatory molecule in T-cell mediated cytotoxicity [14]; the contribution of this adhesive molecule to the host's immune response led to the suggestion that the derangement of the ICAM-1 expression could also be correlated to the cancerous process, as cancer is in fact a cascade of reactions closely connected to the loss of normal immune surveillance. Derangement in the architectural structure of the ICAM-1 or significant alterations in the concentration of its soluble form has been positively related to breast cancer [15], hematologic malignancies [16, 17], gastrointestinal cancer [18] and melanoma [19]. The head and neck cancer is today a field of intense research worldwide. The evolution of diagnostic methods and therapeutic techniques has failed to ameliorate the prognostic indexes of the

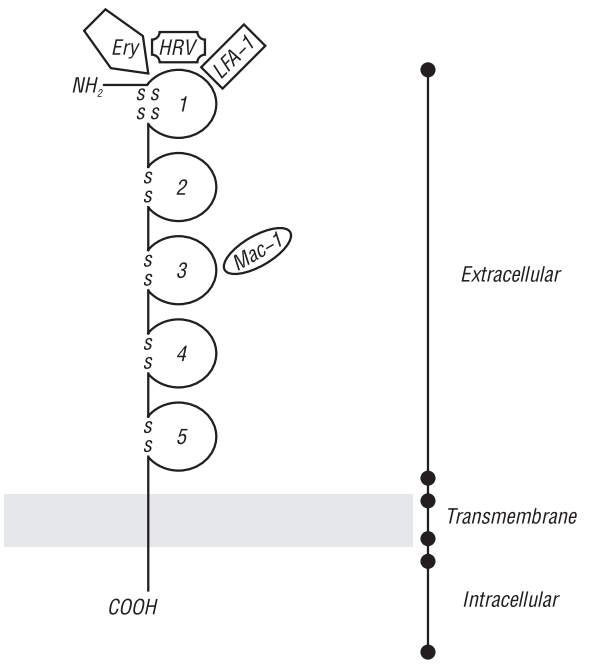

Figure. Structure of ICAM-1 and binding sites for the main ligands of the molecule

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disease during the last three decades. New molecules are constantly sought in the endless armamentarium of molecular biology, in an attempt to contribute to the diagnosis of the disease and establish novel prognostic tools. In the particular case of ICAM-1, the study of this molecule in relation to cancer presents a distinct advantage: as a soluble form of the protein circulates in human serum, commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kits can be used to estimate the concentration instead of the more complicated immunostaining methods which are also dependent on surgical therapies [20]. The idea of a novel molecular index easily estimated from the serum of the patient before and after therapeutic approach has pushed the research efforts mainly towards the direction of the circulating form of the molecule.

Although the term "head and neck" cancer includes every neoplasm developing in the certain anatomic region, the most common use of this specific term is related to the head and neck squamous cell carcinoma, covering more than 90% of these tumours. Based on the knowledge that ICAM-1 is one of the natural ligands to the LFA-1 molecule expressed on leukocytes, and also to a suggested association of this intracellular adhesion molecule's increased serum levels to malignancy [21], many researchers attempted to study the role of ICAM-1 in squamous carcinoma of the head and neck. In assays concerning cultured cell lines, it seems that ICAM-1 expression varies greatly *in vitro* from one experiment to another [22]. This variability, sometimes considered as the result of culture conditions influence makes it difficult to determine its importance as a marker on tumor cells [23]. In oral squamous cell carcinoma the circulating ICAM-1 was not found to be elevated in sera of patients compared to sera of normal controls [24], although in a small (n = 22) specimen of patients with laryngeal carcinoma, a statistically significant decrease was noted [25]. To further complicate things, another study shows a strong positive correlation between increased levels of soluble ICAM-1 in sera of patients suffering from laryngeal cancer and healthy controls mainly regarding the advanced stages of the disease [26]. The research in this field is still in the begining, nevertheless the known interaction of ICAM-1 with fibrinogen of the extracellular matrix factor hyaluronan excites the interest for further elucidation of the role of this molecule in dissemination and metastasis of squamous cell carcinoma [27]. Still, the ICAM-1 seems to be absent in normal epidermal cells; as it is mainly expressed in leukocytes and endothelial cells, it is suggested that the possible useful implementations of the developing knowledge about this molecule, will originate from the study of neoplasms of non-squamous origin. The head and neck is also a common anatomic site for the appearance of malignancies of lymphic tissue, mainly Hodgkin disease and non-Hodgkin lymphomas. The nasopharyngeal carcinoma is also a well-studied tumor characterised by both a squamous and a lymphic component. Over-expression of the ICAM-1 in specimens of malignant tissue combined with increased serum levels of the soluble form were detected in Hodgkin disease [28] usually firstly identified as nodal disease of the head and neck or mediastinum. Regarding the non-Hodgkin lymphomas of the head and neck, the variable forms of this disease and the multiple possible cells of origin make the extraction of conclusions an arduous task. It appears that the serum ICAM-1 levels are associated with poor prognosis of this malignant entity; in addition the normalisation of the soluble ICAM-1 levels follow the complete remission of the disease, whereas a new increase of this molecule concentration in serum is noted in relapses [29]. A novel molecular marker, demonstrating the progression of head and neck non-Hodgkin lymphoma may arise from these efforts, reflecting essentially the shedding of intercellular adhesion molecules from damaged endothelial cells or lymphoma cells into serum in the angiodestructive lymphoreticular region of the tumor. These conclusions are also confirmed in studies concerning other anatomic sites of the non-Hodgkin malignancies [30, 31] as the non-Hodgkin lymphoma is a haematologic entity mainly characterised by a systemic appearance.

The nasopharyngeal carcinoma is a malignant tumor of the upper respiratory tract with an interesting pathologic appearance, as mentioned above, a combination of lymphoid and epithelial elements. Although rare in the western world, this neoplasm is very common in south-eastern Asia, mainly in Chinese population where a genetically determined predisposition is known to exist. The research in this direction, in a starting point yet, still has some challenging results to demonstrate: it seems that the ICAM-1 concentration shows a significant elevation in the sera of patients with nasopharyngeal carcinoma compared to healthy controls and compared to patients suffering from the squamous origin laryngeal and oral cancer [25]. The usefulness of the intercellular adhesion molecules as molecular markers in the lymphoid tissue neoplasms coming dimly into sight today, could easily lead to the hypothesis that the above results are an outcome strongly associated to the lymphoid element of the disease. Although probably a simplified statement, this hypothesis could direct the further research efforts concerning the ICAM-1 more towards nasopharyngeal carcinoma than the head and neck squamous cell carcinoma. To this direction, the increased levels of soluble ICAM-1 were found to correlate with recurrence and poor prognosis of nasopharyngeal carcinoma [32]. The exact role of these adhesion molecules in the genesis and dissemination of the disease is still unknown; a possible association of ICAM-1 with the TATE phenomenon (tumor associated tissue eosinophilia) which appears in nasopharyngeal cancer, was found to be a misleading idea [33] whereas a relation of the ICAM-1 decrease to the Epstein — Barr virus genome commonly detected in NPC is still under investigation. A main axis in this latter field is that an increased expression of ICAM-1

in Epstein — Barr positive malignant cells may be related to the loss of the host's immunosurveillance leading to the progress and dissemination of the disease [34]. A group of latent membrane proteins encoded by the Epstein — Barr virus genome and expressed in nasopharyngeal carcinoma cells seem to be associated to the overexpression of intercellular adhesion molecules in the cellular membrane leading to the change of the adhesive properties of the above cells [35]. In particular, the Ebstein — Barr virus genome is almost ubiquitously identified in a certain type of nasopharyngeal carcinoma, the undifferentiated nasopharyngeal carcinoma (U-NPC) or lymphoepithelioma counting for a high proportion of these tumours. In this NPC subtype, the overexpression of ICAM-1 in neoplastic cells is suggested to have a role in the recruitment of lymphocytes intratumorally [36] leading to the characteristic histological appearance of the neoplasm: a prominent inflammatory infiltrate rich in lymphocytes. Interestingly, a similar mechanism connected to the overexpression of the intercellular adhesion molecule in basal epithelial cells of the crypts of palatine tonsils seems to characterise the intraepithelial lymphocytes migration during inflammation of these tissues [37].

The cancer of the thyroid gland is also a promising field concerning the use of soluble ICAM-1 as a molecular index in serum. Much different in histologic patterns than the other neoplasms of the head and neck, this malignancy appears in four major clinicopathologic types: the papillary, follicular, anaplastic and myeloid carcinoma. An upregulation of soluble ICAM-1 in thyroid cancer patients comparing to normal controls independently of the cancer type was demonstrated in a study [38], and the same results where confirmed in another study limited to a patient group suffering from the papillary form of the disease [39] whereas the apical surface of the thyroid papillary carcinoma cell is found to have the main expression of ICAM-1 by immunohistochemical means [40]. Early studies of the molecular mechanisms of these phenomena have correlated the intercellular adhesion molecule' s upregulation in thyroid cancer to the function of the protein kinase pathway (PKP) suggesting that this physiologic pathway has an important role in the progress and dissemination of thyroid cancer [41]. Although in the starting point yet, the soluble ICAM-1 seems to have many chances to be established as a useful marker for the evaluation of thyroid malignancies. Because of the many different histologic and clinical properties of this neoplasm comparing with the other malignancies of the head and neck, a further reference is out of the intention of this mini-review.

The rare malignancies of the head and neck are reasonably secondary research targets. Nevertheless studies in some tumours with unique characteristics may help the generalization of some main conclusions or may give birth to new research pathways. One such tumour is the adenoid cystic carcinoma of the head and neck, characterised by a slow but relentless progression over a number of years, a late recurrence and a high rate of distant metastastic foci. In this malignancy, an immunohistochemically detected downregulation was found to coexist with increased incidence of late distant metastasis and poor prognosis [42]. In another study, the up-regulation of ICAM-1 displayed significant relationship to the adenoid cystic carcinoma with metastatic lymph node or local recurrence [43]. The rareness of these tumors and controversial results from another study regarding the role of the ICAM-1 molecule in adenoid cystic carcinoma [44] make any conclusion precarious. It should also be mentioned that a higher level of soluble ICAM-1 was closely associated with impaired T-cell dependent immune functions assessed by delayed-type hypersensitivity skin reactions, and with the relapse of a rare non-Hodgkin lymphoma named lethal midline granuloma [29] appearing as an efficient parameter for the monitoring and evaluation of the disease course.

The adhesion molecules are today the focus of the scientific interest worldwide. The numerous members of this group are under investigation for their participation in cell adhesion, inflammation and cancer. Because of the continuously arising information about the importance of role of these molecules in physiologic and pathophysiologic processes of the human body, we believe that a review of the current literature concerning each of these molecules would be a challenging essay, valuable for the researcher and therefore, worth while. In particular, ICAM-1 is a member of the immunoglobulin adhesion molecules superfamily with multiple possible useful implementation in diagnosis and clinical evaluation of head and neck cancer. Many parameters still have to be clarified concerning this molecule; the present studies are few, usually with small samples, whereas the co-participation of many other factors makes thorny the illumination of its role in the neoplasmatic process. It seems therefore, that ICAM-1 will play a leading part in the research of cancer in the forthcoming years interesting and valuable tools for the diagnosis and prognosis of head and neck cancer will hopefully ensue from these efforts.

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РОЛЬ МОЛЕКУЛЫ МЕЖКЛЕТОЧНОЙ АДГЕЗИИ ICAM-1 ПРИ РАКЕ ГОЛОВЫ И ШЕИ

Молекулы межклеточной адгезии (ICAM-1), являющиеся продуктом гена — члена суперсемейства генов иммуноглобулинов, экспрессированы в клетках многих тканей человека и принимают участие в ряде физиологических и патофизиологических процессов. В мини-обзоре обобщены последние данные доступной литературы об изменении уровня экспрессии ICAM-1 при раке головы и шеи, а также обсуждены возможности применения знаний о молекулах адгезии в области диагностики и прогноза заболевания.

Ключевые слова: **молекулы адгезии, молекула межклеточной адгезии ICAM-1, рак ротовой полости, рак головы и шеи.**