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Ectoenzymes in Epithelial Ovarian Carcinoma: Potential Diagnostic Markers and Therapeutic Targets

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1. Introduction

Ovarian cancer is one of the most lethal among the gynaecological malignancies, affecting 1-2% of women in developed countries (Cannistra, 2004). The lethality of ovarian cancer is primarily attributable to our current inability to detect the disease at an early stage, when it is still limited to the ovary. Therefore, the majority of patients are diagnosed when they have advanced-stage disease. Despite progresses in cytotoxic therapies, only 30% of patients with advanced-stage ovarian cancer survive 5 years after diagnosis. The insidious nature of ovarian cancer stems from its unique biological behaviour: ovarian carcinoma can spread by direct extension to adjacent organs, and exfoliated tumour cells can be transported in peritoneal fluid (Naora et al., 2005). Subsequent implants are characterised by their adhesion to mesothelial cells, migration throughout and invasion of the tumor cells into the omentum and peritoneum. This seeding of the peritoneal cavity is frequently associated with ascites formation. Only secondarily and rather late during the disease progression, are pelvic and para-aortic lymph nodes involved. However, the local peritoneal disease cannot be controlled and remains a factor leading to death (Feki et al., 2009). The cellular processes that lead to local and distant dissemination of ovarian cancer are not fully understood, and the mechanisms of interaction between cancer cells and mesothelium need to be further elucidated to achieve novel information on the biology of this highly aggressive form of cancer and possibly, to identify new potential targets for selective therapeutic strategies.

The combined effort of clinicians and researchers has led to the identification of a number of molecules that might facilitate screening, diagnosis, prognosis and monitoring response to treatment or relapse during follow-up. These new molecules might provide specific targets for anti-tumour therapy with antibody-directed treatments, gene therapy or specific inhibitory molecules. An unexpectedly high number of these newly identified molecules have turned out to be cell surface-expressed ectoenzymes. Ectoenzymes are a large, heterogeneous class of membrane proteins whose catalytically active sites face the extracellular environment. The products of their catalytic activities can influence the extracellular environment (for example, several of these products can function as second messengers or regulate the recruitment of cells). Moreover, many ectoenzymes can function

both as receptors and signalling molecules through mechanisms that are independent from their catalytic activity. The nomenclature of ectoenzymes is confusing: in addition to several original descriptive names, many of them also have a cluster designation (CD) given by immunologists and an EC number assigned by biochemists.

This chapter presents an overview of the ectoenzymes involved in ovarian cancer biology, development or progression (focusing on CD10, CD13, CD26, CD73, CD157, and Autotaxin/CD203c) and highlights the potential role of these molecules as markers for ovarian cancer outcome or as novel therapeutic targets.

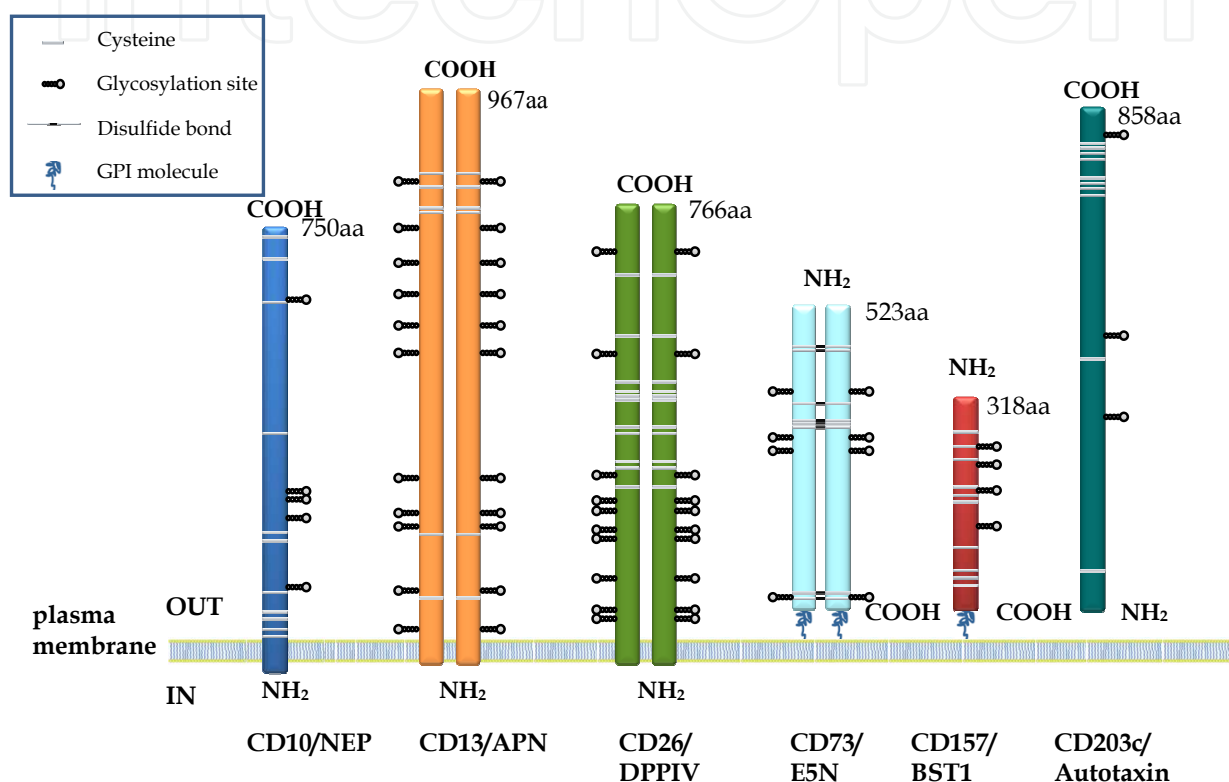


Fig. 1. Schematic representation of ectoenzymes involved in ovarian cancer progression.

2. CD10

2.1 Structure and expression

Human CD10 (also known as CALLA, NEP, Neprilysin, EC 3.4.24.11) is a 100 kDa cell surface aminopeptidase originally characterised as a T cell differentiation antigen (Common Acute Lymphoblastic Leukaemia Antigen, CALLA) identified for its expression in most acute lymphoblastic leukaemias (Shipp et al., 1989). Subsequently, its identity with neutral endopeptidase 24.11 (NEP) and KII-NA was unequivocally established and a wider distribution attributed to the protein (Shipp et al., 1993).

The CALLA/NEP gene spans more than 80 kilobases (kb) on chromosome 3q21-q27 and is composed of 24 exons (D'Adamio et al., 1989). CD10 is a 749-amino acid type II integral membrane glycoprotein with a single 24-amino acid hydrophobic segment that can function both as a transmembrane region and a signal peptide. The COOH-terminal is composed of 700-amino acids and forms the extracellular protein fragment, whereas the 25 amino-

terminal amino acids form the cytoplasmic tail (Ritz et al., 1980). CD10 is expressed by human lymphoblastic leukaemia cells, by early lymphoid progenitors (Greaves et al., 1983; Hoffmann-Fezer et al., 1982) and by other lymphoid malignancies (Greaves, et al., 1983). It is also expressed in terminally differentiated granulocytes and in non-lymphoid cells, including cultured fibroblasts and bone marrow stromal cells, implying that its biological function is not restricted to lymphoid development (Pesando et al., 1983). CD10 expression has been reported on epithelial cells of various tissues, such as bronchial epithelial cells, renal proximal tubular epithelial cells, small intestinal epithelium, biliary canaliculae (Loke et al., 1990), breast myoepithelium (O'Hare et al., 1991), prostate, endometrium (Suzuki et al., 2001) and placenta (Ino et al., 2000). Several reports have shown that CD10 is also expressed in selected solid tumours of the colon (Fujimoto et al., 2005), lung (Cohen et al., 1996), breast (Burns et al., 1999), prostate (Dai et al., 2001) and ovary (Khin et al., 2003).

2.2 Functions

CD10 is a cell membrane-associated zinc metalloproteinase that cleaves peptide bonds on the amino-terminal side of hydrophobic amino acids and inactivates a variety of peptides, cytokines and hormones (Shipp et al., 1988). CD10 plays an important role in the maintenance of homeostasis in normal tissues by degrading endothelin-1 (ET-1), enkephalin, oxytocin, neurotensin, bradykinin, bombesin-like peptides, and angiotensin I and II, among others (Erdos et al., 1989). In specific contexts, CD10 works in concert with CD13, BP-1 and CD26 to digest common substrates (Bowes et al., 1987). This enzyme network controls the local concentrations of these substrates, thus regulating their biological activities and the downstream signal transduction pathways (Shipp & Look, 1993).

CD10 has been implicated in a variety of processes including stromal cell-dependent B lymphopoiesis (Salles et al., 1992), chemotactic and inflammatory responses (Madara et al., 1993), and T cell activation (Massaia et al., 1988). Apart from the hematopoietic compartment, CD10 participates in the final stage of peptide hydrolysis in the renal proximal tubules and the small intestine.

Several reports showed that CD10 plays a role in neoplastic transformation and tumour progression in selected human malignancies by inactivating ET-1 or bombesin, both involved in autocrine/paracrine stimulation of tumour cell proliferation and migration in many epithelial cancers, including breast (Burns, et al., 1999), lung (Cohen, et al., 1996) and prostate cancers (Dai, et al., 2001).

CD10 is expressed in the stroma of malignant ovarian carcinomas, but not in benign adenomas or in normal ovaries, and its expression inversely correlates with histologic tumour grade (Khin, et al., 2003). In ovarian carcinoma, ET-1 promotes cell growth, invasion and angiogenesis by acting as an autocrine/paracrine growth factor (Bagnato et al., 1999; Salani et al., 2000). CD10 may directly influence the local concentration of ET-1 via its enzymatic activity thus contrasting the mitogenic effects of ET-1, suggesting that CD10 plays a role in the biology of neoplastic transformation or in the control of ovarian cancer progression (Kajiyama et al., 2005). It has been suggested that CD10 may function as a tumour suppressor factor in ovarian cancer progression, as well as in lung and prostate cancer (Papandreou et al., 1998).

In addition to its role in the control of ovarian carcinoma progression, Kajiyama et al. (Kajiyama, et al., 2005) demonstrated that CD10 enhances susceptibility to paclitaxel in the SKOV3 ovarian carcinoma cell line, resulting in increased apoptosis and reduced tumour formation and invasiveness in *in vivo* models. This evidence suggests that CD10 might serve as

a potential target for gene therapy in metastatic ovarian carcinoma. However, no experimental data in this regard is so far available, and this aspect deserves further investigation.

3. CD13

3.1 Structure and expression

Human CD13 was isolated in 1963 from pig kidney (Pfleiderer et al., 1963) and is a transmembrane protein also known as aminopeptidase N (APN), alanine aminopeptidase, microsomal aminopeptidase, amino oligopeptidase, GP150. CD13 cleaves N-terminal neutral amino acids of a number of peptides and proteins. The CD13 gene is located on the long arm of chromosome 15 and the coding sequence spans 20 exons (Lerche et al., 1996). CD13 consists of 967 amino acids constituting a short N-terminal cytoplasmic domain, a single transmembrane fragment and a large ectodomain encompassing the active site (Olsen et al., 1988).

The CD13 protein is predominantly expressed in stem cells and cells of the granulocytic and monocytic lineages at discrete stages of differentiation (Razak et al., 1992). Non-hematopoietic cells, such as renal proximal tubular epithelial cells, small intestinal epithelium, biliary canaliculae, bone marrow stromal cells, fibroblasts and osteoclasts are also CD13-positive (Metzgar et al., 1981; Noren, 1986). Deregulated expression of membrane and/or soluble forms of CD13 has been observed in many diseases. For example, CD13 is overexpressed in acute and chronic myeloid leukaemias (Antczak et al., 2001) and in anaplastic large cell lymphomas (Dunphy et al., 2000). High expression of CD13 has been detected in various solid tumours such as melanoma (Fujii et al., 1995), renal (Kitamura et al., 1990), pancreas (Ikeda et al., 2003), colon (Hashida et al., 2002), prostate (Ishii et al., 2001a), gastric (Carl-McGrath et al., 2004), thyroid (Kehlen et al., 2003) and ovarian cancers (Yamashita et al., 2007). In ovarian cancer CD13 expression is associated with the histological subtype: over 80% of serous and mucinous carcinomas but only 20% of clear cell carcinomas are CD13-positive (van Hensbergen et al., 2004). Moreover, CD13 also exists as a soluble form, likely originating from shedding of the membrane protein, which has a potent enzymatic activity in the plasma and reactive effusions of cancer patients, such as ascites from ovarian cancer patients (van Hensbergen et al., 2002).

3.2 Functions

CD13 is a multifunctional protein acting as an enzyme, a receptor and a signalling molecule. As an enzyme, CD13 regulates the activity of numerous peptides involved in important biological processes by removing their N-terminal aminoacids, mainly neutral aminoacids (Noren, 1986). CD13 hydrolyses the N-terminal Arg of angiotensin III to generate angiotensin IV (Danziger, 2008) and participates in the metabolism of glutathione, somatostatin, thymopentin, neurokinin A, splenopentin, nociceptin FQ and peptides derived from the thrombin receptor (Noble et al., 1997). In the intestinal brush border, the CD13 enzymatic domain faces the lumen and has been supposed to play an important role in the final stages of the digestion of small peptides (Semenza, 1986). CD13 has been postulated to cooperate with CD10 in the hydrolysis of oligopeptides in the small intestine (Semenza, 1986), and to inactivate opioid peptides and enkephalins in the brain (Matsas et al., 1985) and the chemotactic peptide Met-Leu-Phe during neutrophil-mediated inflammatory responses (Connelly et al., 1985).

CD13 also acts as a receptor for coronaviruses, which exploit the endocytosis of the molecule to enter into respiratory and intestinal epithelial cells (Nomura et al., 2004). Moreover, CD13 is involved in transduction of intracellular signals, converging on mitogen-activated protein kinases, such as ERK1/2, JNK, and p38, in association with auxiliary proteins such as galectin-3 (Santos et al., 2000), galectin-4 (Danielsen et al., 1997), RECK (Miki et al., 2007) and the tumour-associated antigen L6 (Chang et al., 2005).

CD13 activates or inactivates bioactive peptides on the cell surface, thus regulating their activities on adjacent cells. CD13 has a wide range of functions, including a role in antigen presentation by processing antigenic peptides protruding from MHC class II molecules (Larsen et al., 1996), in phagocytosis (Mina-Osorio et al., 2005), in lymphocyte and monocyte adhesion and aggregation (Mina-Osorio et al., 2006) and intracellular signal transduction (Santos, et al., 2000), in stem cell differentiation (Chen et al., 2007), cholesterol uptake (Knopf et al., 2007) and spermatozoid motility (Carlsson et al., 2006).

Several studies have confirmed a correlation between CD13 expression and increased malignant behaviour in melanoma (Carlsson, et al., 2006), prostate (Ishii, et al., 2001a), colon (Hashida, et al., 2002) and lung cancers (Chang, et al., 2005). In these tumours it is implicated in cell motility and in the degradation of and invasion through the extracellular matrix (ECM) (Saiki et al., 1993). By contrast, an inverse correlation has been reported between CD13 expression and tumour progression in renal cancer (Ishii et al., 2001b).

Several studies have demonstrated that CD13 expression is induced in tumour microvascular endothelial cell by angiogenic cytokines and hypoxia and that it regulates endothelial cell tube formation both in *in vitro* (Hashida, et al., 2002) and in *in vivo* models (Bhagwat et al., 2001).

Functional studies indicate that CD13 expression is associated with a long spindle fibroblast-like morphology and a migratory phenotype accompanied by enhanced secretion of MMP-2 in various ovarian cancer cell lines (Terauchi et al., 2007). Since CD13 is involved in cell motility, in the invasive potential of tumour cells and in the neoangiogenic processes, it holds promise as a therapeutic tumour target. In ovarian cancer it has been demonstrated that suppression of CD13 activity by specific inhibitors (including blocking antibodies, bestatin or actinonin) reduces the proliferative, migratory and angiogenic potential of tumour cells, as well as the peritoneal dissemination *in vivo* in mouse models, leading to prolonged survival (Terauchi, et al., 2007). It has also been determined that CD13 is involved in the chemosensitivity and radiosensitivity of ovarian cancer cells. Indeed, combined treatment of tumour cells with bestatin and paclitaxel showed a significant increase in apoptosis and an improved outcome of ovarian cancer patients (Yamashita, et al., 2007).

Taken together, the results from these studies suggest that inhibition of CD13 enzymatic activity may provide a new approach for improving the efficacy of ovarian carcinoma therapy, leading to reduced cell proliferation, motility, invasiveness, angiogenesis and chemoresistance of ovarian cancer cells.

4. CD26

4.1 Structure and expression

CD26, also known as dipeptidyl peptidase IV (DPPIV), adenosine deaminase binding protein (ADA bp) or EC 3.4.14.5, is a multifunctional type II cell surface glycoprotein. CD26 is a 110 kDa aminopeptidase that is catalytically active only as a dimer. Each monomer consists of two domains, an α/β -hydrolase domain (residues 39–51 and 501–766) and an

eight-blade β -propeller domain (residues 59–497), that enclose a large cavity of $\sim 30\text{--}45\text{\AA}$ in diameter. Access to this cavity is provided by a large side opening of $\sim 15\text{\AA}$ (Aertgeerts et al., 2004). However, only elongated peptides, or unfolded or partly unfolded protein fragments, can reach the small pocket within this cavity that contains the active site. The main enzymatic activity of CD26 is a serine protease activity with a post-proline dipeptidyl aminopeptidase activity, preferentially cleaving Xaa-Pro or Xaa-Ala dipeptides (where Xaa is any amino acid except Pro) from the N-terminus of polypeptides.

CD26 contains nine potential N-linked glycosylation sites that lie predominantly on the propeller domain, near the dimerization interface (Engel et al., 2003). The human CD26 gene consists of 26 exons and is located on the long arm of chromosome 2 (Tanaka et al., 1992).

4.2 Functions

CD26 exerts pivotal roles in nutrition, metabolism, immune and endocrine systems, bone marrow mobilization, cancer growth and cell adhesion. CD26 activates or deactivates various bioactive peptides on the cell surface or in the extracellular environment, by cleaving them enzymatically, therefore regulating their availability for adjacent cells. CD26 substrates include cytokines and several chemokines: substance P, chorionic gonadotropin, tumour necrosis factor α (TNF- α), interleukin-2, stromal cell-derived factor 1a, RANTES, neuropeptide Y, peptide YY, glucagon-like peptide (GLP)-1, GLP-2 and glucose-dependent insulinotropic peptide (Gorrell, 2005). Besides its enzymatic activity, CD26 shows a variety of functions, including regulation of inflammatory and immunological responses, signal transduction, interactions with extracellular matrix proteins and apoptosis.

CD26 ligands include adenosine deaminase (ADA) (Morrison et al., 1993), kidney Na⁺/H⁺ ion exchanger 3 (Girardi et al., 2001) and fibronectin (Cheng et al., 2003).

CD26 has been consistently associated with cancer since its identification (ten Kate et al., 1984). A number of recent studies have provided evidence that CD26 plays a role in discrete steps of tumour progression, such as cell adhesion, invasion and cell cycle arrest (Pethiyagoda et al., 2000). In selected carcinoma tissues, CD26 is misexpressed and it can function either as an oncogene or as a tumour suppressor gene. Its expression is upregulated and associated with tumour aggressiveness in T and B lymphomas and leukaemias (Bauvois et al., 1999; Carbone et al., 1995; Dang et al., 2003), thyroid follicular tumours (de Micco et al., 2008), papillary carcinomas, astrocytic tumours (Stremenova et al., 2007) and gastrointestinal stromal tumours (Yamaguchi et al., 2008). Conversely, loss of CD26 occurs during malignant transformation of melanocytes into melanoma (Wesley et al., 1999), indicating a possible role of the molecule in suppressing the malignant transformation of melanocytes.

The precise biological mechanism through which CD26 regulates tumour cell progression remains controversial. According to Wesley et al., high CD26 expression leads to a loss of tumorigenicity through its serine protease activity (Wesley, et al., 1999). On the other hand, the suppressive effect of CD26 on melanoma's malignant phenotype is related neither to the protease activity located at the extracellular domain nor to the signal transduction related to the cytoplasmic domain (Pethiyagoda et al., 2000).

In 2002 Kajiyama et al. first described the expression of CD26 in ovarian carcinoma cell lines and tissues. CD26 immunoreactivity was observed on surgically resected ovarian carcinoma of different histotypes, but was not found in stromal cells. CD26 expression in ovarian cancer cell lines is associated with an epithelioid morphology. Indeed, forced expression of

CD26 in an ovarian cancer cell line results in marked morphological changes from a fibroblastic/spindle-shaped appearance toward an epithelioid pattern, which is paralleled by the shift from mesenchymal to epithelial markers (Kajiyama et al., 2002).

Exogenous expression of CD26 leads to a significant reduction in the invasive potential in ovarian carcinoma cell lines *in vitro* and an increased E-cadherin expression. Indeed, CD26 expression in ovarian cancer cell lines positively correlates with E-cadherin expression and induces the upregulation of both E-cadherin and β -catenin, which play a key role in the suppression of invasive and metastatic phenotype of cancer cells (Kajiyama et al., 2003). Moreover, in ovarian carcinoma cell lines CD26 expression negatively correlates with MMP-2 expression, and the expression levels of both MMP-2 and MT1-MMP are significantly reduced in CD26-transfected cells. Overexpression of CD26 also increases expression levels of TIMP-1 and TIMP-2, known to be key inhibitors of tumour invasion, angiogenesis and metastasis (Kikkawa et al., 2005).

Overexpression of CD26 reduced intraperitoneal dissemination of carcinoma cells and prolonged survival time *in vivo* in a mouse orthotopic model. Ovarian carcinoma cell lines with higher CD26 expression has significantly less metastatic potential when injected into the abdominal cavity of nude mice than the CD26-negative control cells (Mizutani et al., 2003). Consistent with this, the intensity of CD26 immunohistochemical staining in tissues proved to be stronger in well-differentiated and non-infiltrating ovarian carcinomas, thus indicating that the decrease of CD26 is related to neoplastic transformation and tumour progression (Zhang et al., 2008).

A positive correlation between CD26 expression and sensitivity to paclitaxel has been described in several ovarian carcinoma cell lines. Forced expression of CD26 in a CD26-negative ovarian cancer cell line significantly enhanced sensitivity to paclitaxel by increasing the rate of apoptotic cells through the repression of the transcriptional factor Twist, a master regulator of epithelial-mesenchymal transition, linked to paclitaxel resistance. These data were corroborated by the observation that paclitaxel-resistant NOS-PR cells showed reduced expression of CD26. However, no significant alteration in paclitaxel sensitivity was observed in the presence of a specific inhibitor of DPPIV activity in CD26-transfected or natively CD26-overexpressing cells (Kajiyama et al., 2010).

Further understanding of the anti-invasive effect of CD26 may prove useful in devising new strategies in the control of ovarian cancer and other carcinomas. Like other membrane-bound peptidases, CD26 may soon be destined for use not only as a new diagnostic/prognostic marker, but also as a molecular target in novel therapeutic strategies.

5. CD73

5.1 Structure and expression

CD73, also known as ecto-5'-nucleotidase (ecto-5'-NT), is a glycosylphosphatidylinositol (GPI)-anchored ectoenzyme composed of two identical subunits of 70-74 kDa. The mature protein consists of 548 amino acids and corresponds to a molecular mass of ~63 kDa (Airas et al., 1993). The human CD73 gene has been mapped to region q14-q21 of chromosome 6. CD73 is abundantly expressed by vascular endothelial cells (Jalkanen et al., 2008) and by a subpopulation of peripheral blood lymphocytes represented by regulatory T cells and primed uncommitted CD4-positive T cells. Follicular dendritic cells (Airas, 1998), intestinal epithelial cells (Strohmeier et al., 1997), fibroblasts (Nemoto et al., 2004), cardiomyocytes

(Carneiro-Ramos et al., 2004), neurons, oligodendrocytes (Maienschein et al., 1996) and mesenchymal stem cells (Barry et al., 2001) have been reported to express CD73.

5.2 Functions

It has been proposed that CD73 behaves as an adhesion molecule modulating lymphocyte-endothelial cell interactions (Airas et al., 2000). Furthermore, CD73 is known to play a critical role *in vivo* in maintaining the integrity of the vascular endothelium during hypoxia (Colgan et al., 2006), in mediating efficient entry of lymphocytes into the central nervous system during experimental autoimmune encephalomyelitis and in regulating leukocyte-endothelium interaction during cardiac ischemia-reperfusion (Koszalka et al., 2004).

CD73 catalyzes the dephosphorylation of purine and pyrimidine ribo- and deoxyribonucleoside monophosphates to the corresponding nucleoside. This ectoenzymatic cascade operates in tandem with CD39 (ecto-ATPase) and catalyzes the conversion of AMP to bioactive adenosine from adenosine triphosphate (ATP) which is often released into the extracellular environment from damaged or inflamed target cells (Stagg et al., 2010b). Extracellular adenosine induces potent immunosuppressive effects, mainly mediated through four adenosine-binding G protein-coupled receptors. In addition to its enzymatic function, CD73 has been suggested to have a role in T cell signalling (Resta et al., 1998).

The resistance of many solid tumours to host immune responses has been largely attributed to a spectrum of tumour-associated immune-suppressive mechanisms. During tumour progression, tumour cells promote a tolerant microenvironment and activation of multiple immunosuppressive mechanisms, which may act in concert to attenuate an effective immune responses (Rabinovich et al., 2007). It is thought that tipping the balance from an immune-suppressive to an immune-active environment is necessary for effective cancer immunotherapy (Rabinovich et al., 2007). Adenosine is a purine nucleoside reaching high concentrations within solid tumours (Ohta et al., 2006) where it promotes tumour growth through the stimulation of tumour angiogenesis (Stagg & Smyth, 2010b) and inhibition of anti-tumour immune responses (Hoskin et al., 2008). However, the mechanisms whereby adenosine accumulates in solid tumours and the effects resulting from this accumulation are not completely understood.

CD73 expression has been reported in several tumour types (Stagg & Smyth, 2010b), including ovarian cancer (Jin et al., 2010) and its expression has been associated with a prometastatic phenotype in melanoma and breast cancer (Leth-Larsen et al., 2009). Although *in vitro* studies suggested that CD73 expression can enhance breast cancer cell migration and invasion, the underlying mechanisms remain elusive. In breast cancer cells, CD73 expression significantly inhibits endogenous adaptive anti-tumour immunosurveillance, in addition, CD73-derived adenosine enhances tumour cell migration *in vitro* and metastasis *in vivo* through the activation of A2B adenosine receptors (Stagg et al., 2010a). CD73 expression has been shown to be regulated by estrogen receptors, whereby loss of estrogen receptors significantly enhances CD73 expression (Spychala et al., 2004). CD73 is highly expressed in many human solid tumours (Salmi et al., 2011), and its high expression and activity are associated with tumour invasiveness and metastasis (Stagg et al., 2010a) and with shorter patient survival. Recently it has been demonstrated that exosomes released by cancer cells *in vitro* and in biological effusions are able to dephosphorylate exogenous ATP and 5'AMP to form adenosine. These hydrolytic activities have been in part attributed to expression of functional CD39 and CD73 by exosomes. This mechanism may contribute to augmenting

adenosine levels within the tumour microenvironment and hence participate to the negative regulation of T cell function (Clayton et al., 2011).

CD73 expressed in ovarian cancer negatively modulates tumour antigen-specific T cell immunity. Indeed, it has been demonstrated that knockdown of CD73 on tumour cells by siRNA improved anti-tumour T cell responses, completely restoring the efficacy of adoptive T cell therapy and leading to long-term tumour-free survival in tumour-bearing mice. Moreover, in a mouse model, host CD73 deficiency decreased the ovarian carcinoma burden and increased mouse survival in a T cell-dependent manner. Accordingly, reduction of both tumour and host CD73 resulted in an optimal anti-tumour effect (Jin et al., 2010).

Pharmacological blockade of CD73 using the specific inhibitor α,β -methylene adenosine 5'-diphosphate (APCP) or a blocking anti-CD73 monoclonal antibody inhibited tumour growth and promoted efficacy of adoptive T cell therapy (Zhang, 2010), suggesting that CD73-targeted therapy might be a promising and rational approach to cancer treatment (Häusler SF et al., 2011). In summary, detailed analysis of CD73 expression on tumour cells and/or host cells regulating anti-tumour immunity may have important consequences on our understanding of immunosuppressive mechanisms in the tumour microenvironment that support tumour evasion. Inhibition of CD73 could be a therapeutic adjuvant to improve cancer immunotherapy.

6. CD157

6.1 Structure and expression

CD157/BST-1 is a GPI-anchored glycoprotein encoded by a member of a gene family of NADase/ADP-ribosyl cyclase, which includes CD38. The CD38 and bone marrow stromal cell antigen 1 (BST-1) genes arose by gene duplication before the divergence of humans and rodents (Ferrero et al., 1997). The human CD157 gene is located on chromosome 4p15, it spans ~35 kb and consists of nine exons (Muraoka et al., 1996). Although CD157 was initially characterised as a stromal (Kaisho et al., 1994) and myeloid surface antigen (Goldstein et al., 1993), it is also expressed by certain other cell types that include vascular endothelial cells (Ortolan et al., 2002) and mesothelial cells (Ross et al., 1998).

6.2 Functions

CD157 is an ectoenzyme that cleave extracellular nicotinamide adenine dinucleotide (NAD) and NADP⁺, generating cyclic ADP ribose (cADPR), NAADP⁺, and ADPR. Beside their role as mediators of intracellular calcium release (Galione, 1994), the products of CD157-operated NAD cleavage can act as extracellular immunomodifiers (Haag et al., 2007). Emerging data indicated that these metabolites can act extracellularly as paracrine factors (Moreschi et al., 2008). Moreover, the catalytic reactions generate substrate for ADP-ribosyl transferases and polymerases involved in cell signalling, DNA repair and apoptosis (Haag et al., 2007). In addition, CD157 possesses receptor activity, indeed, it interacts with other surface molecules thus acquiring the ability to transduce signals (Malavasi et al., 2008). Accumulating evidence indicates that CD157 is a key molecule in the control of leukocyte adhesion, migration and diapedesis (Funaro, 2004; Ortolan, 2006). CD157 establishes a structural interaction with β 1 and β 2 integrins (Lavagno et al., 2007) and, following antibody-induced cross-linking, promotes their relocation into detergent-resistant membrane domains, thus driving the dynamic reorganization of signalling-

competent membrane microdomains. Moreover, CD157 effectively contributes to the integrin-driven signalling network that is critical during leukocyte transmigration (Lo Buono et al., 2011).

Recently, we demonstrated that CD157 is expressed in epithelial ovarian cancer (EOC) primary cell cultures and tissues, and it is involved in interactions among EOC cells, extracellular matrix proteins, and mesothelial cells which ultimately control tumour cell migration and invasion. The results inferred *in vitro* were validated by clinical evidence: CD157 was expressed by 93% of EOC analysed and high CD157 expression was associated with rapid tumour relapse in patients. Moreover, CD157 appears to be a marker of poor prognosis in the serous subtype of ovarian cancer, which is the most frequent and aggressive type. Multivariate survival analysis showed that CD157 is an independent prognostic factor of tumour relapse shortly after surgical debulking of ovarian cancer (Ortolan et al., 2010). Several lines of evidence point to the fact that high levels of CD157 are associated with more aggressive ovarian cancer. First, forced expression of CD157 in CD157-negative NIH:OVCA-3 cells substantially increased cell motility, a prerequisite for dissemination. Second, blockade of CD157 activity, either by a specific monoclonal antibody *in vitro* or by its weak expression in patients, was associated with reduced invasion and migration by tumour cells. Finally, clinical observations revealed that high CD157 correlated with rapid tumour relapse (Ortolan et al., 2010). However, how CD157 might contribute to a more aggressive ovarian cancer remains to be defined (Annunziata et al., 2010). Our results support the rationale for the future use of CD157 as a potential diagnostic target for EOC, providing the opportunity to develop new strategies using CD157 as a therapeutic target to prevent tumour dissemination in patients with serous ovarian cancer.

7. Autotaxin/CD203c

7.1 Structure and expression

Autotaxin (ATX) also known as CD203c or ENPP2 (ectonucleotide pyrophosphatase/phosphodiesterase 2), is a cell motility-stimulating factor originally isolated from human melanoma cells (Stracke et al., 1992). It is a member of the ENPP protein family, which includes membrane-associated or secreted ectoenzymes that hydrolyze pyrophosphate or phosphodiester bonds in various extracellular compounds, such as nucleotides and lysophospholipids (Tokumura et al., 2002). ATX/CD203c is a soluble 125 kDa glycoprotein encoded by a single gene located on human chromosome 8. Three alternatively spliced isoforms have been reported: α , β and γ . Isoform β , considered the canonical form, is the predominant one, and is expressed in peripheral tissues while isoform γ is more highly expressed in the central nervous system. Both β and γ variants are catalytically active, whereas the α isoform is rapidly degraded into smaller inactive forms (Giganti et al., 2008). Autotaxin contains a catalytic domain, which is responsible for enzymatic activity and two additional domains, a somatomedin-B-like domain and a nuclease-like domain, which are located at the N-terminus and C-terminus of the protein, respectively. The somatomedin-B-like domain is rich in cysteine residues and contains an RGD tripeptide motif that is possibly involved in cell-extracellular matrix interactions. The nuclease-like domain contains an EF hand-like motif, structurally similar to the DNA- or RNA-non-specific endonucleases but it is catalytically inactive. All three domains are required for the catalytic activity (Nishimasu et al., 2011).

ATX is predominantly expressed in brain, kidney, placenta, ovary, small intestine and in body fluids such as plasma (Tokumura et al., 2002), cerebral spinal fluid, saliva, and follicular and amniotic fluids (Giganti et al., 2008; Nishimasu et al., 2011).

7.2 Functions

Autotaxin is defined as a multi-functional protein producing (i) lysophosphatidic acid (LPA) by conversion of lysophosphatidylcholine (LPC), present in human serum or plasma, and (ii) cyclic phosphatidic acid (cPA), an LPA analogue with distinct physiological activities. ATX activity accounts for the majority of LPA production in blood (Nakanaga et al., 2010). The biological activity of LPA is largely mediated through the activation of five receptors, LPA1 to LPA5. All of these are type I, rhodopsin-like G protein-coupled receptors with seven-transmembrane alpha helices (Lin et al., 2010). LPA evokes a wide variety of cellular responses in different cell types including Ras-mediated cell proliferation and Rho/Rac-regulated cell migration (including vascular endothelial cells migration), neurite retraction, platelet aggregation, smooth muscle contraction, actin stress fibers formation and cytokine/chemokine secretion. LPA levels are increased during pathological conditions of the brain (neuropsychiatric disorders such as bipolar disorders, schizophrenia, etc.). Deregulation of LPA signalling is found in cardiovascular diseases: the formation of excess fibrous connective tissues is strongly influenced by receptor-mediated LPA signalling in different organs (for example, lung, kidney and liver) (Lin et al., 2010). Moreover, in both *in vivo* and *in vitro* systems, LPA has been shown to participate in critical events of cancer progression such as cell proliferation, growth, survival, migration, invasion, and promotion of angiogenesis (van Meeteren et al., 2007). Therefore, LPA signalling is worth considering for its involvement in disease processes as well as in normal physiological functions.

Autotaxin was originally identified as a tumour cell motility factor released in the spent medium of human melanoma cells. When overexpressed in Ras-NIH3T3 cells, ATX promotes tumour aggressiveness, metastasis and angiogenesis in nude mice (Nam et al., 2000). ATX is highly expressed in several human cancers, including glioblastoma, lung and breast cancer, renal cell carcinoma, neuroblastoma, thyroid carcinoma and Hodgkin's lymphoma (Mills et al., 2003). High ATX expression is detected in glioblastoma multiforme, a lethal cancer with a high infiltration rate (Hoelzinger et al., 2005). ATX has also been found upregulated in stromal cells from prostate carcinoma patients (Zhao et al., 2007) and its expression is strongly enhanced by v-Jun oncogene-induced transformation (Black et al., 2004) and by overexpression of cancer-associated $\alpha 6 \beta 4$ integrin in breast cancer (Chen et al., 2005). In an *in vivo* angiogenesis model, ATX-transfected Ras-transformed NIH3T3 cells caused more prominent new blood vessel formation than control cells (Nam et al., 2000). In addition, ATX stimulates human vascular endothelial cells grown on Matrigel to form tubules, similarly to the effects induced by vascular endothelial growth factor (VEGF) (Nam et al., 2001).

Recent studies have demonstrated the molecular mechanisms underlying the ATX/LPA axis in cancer. ATX-induced motility of melanoma cells is mediated through the activation of focal adhesion kinase (FAK) (Jung et al., 2004) and, in the nucleus, by the DNA binding of necrosis factor kappa B (NF- κ B) (Lee et al., 2006).

Another finding is that LPA strongly counteracts Taxol-induced death in the MCF-7 breast cancer cell line and in MDA-MB-435 melanoma cells, by activating phosphatidylinositol 3-kinase (PI3K), which antagonizes the Taxol-induced accumulation of cancer cells in the

G2/M phase of the cell cycle (Samadi et al., 2009). Recently it has been demonstrated that the ATX/LPA axis allows breast cancer cells to escape from mitotic arrest following the PI3K-dependent displacement of Taxol from polymerised tubulin (Samadi et al., 2011). Moreover, recent data from *in vivo* experiments indicate that increased expression of ATX, LPA1, LPA2 or LPA3 receptors in mice is associated with enhanced invasiveness of estrogen receptor-positive, metastatic breast cancers (Liu et al., 2009). Finally, the significance of the plasma or serum ATX levels in cancer patients has been reported in patients with follicular lymphoma, where serum ATX levels proved to be significantly higher than those in healthy subjects, to correlate with plasma LPA levels and to change according to patient clinical course (Masuda et al., 2008). Additional studies have reported an impressive and specific increase in serum ATX activity and plasma LPA in patients with chronic hepatitis C (Watanabe et al., 2007) and pancreatic cancer (Nakai et al., 2011).

In the last 20 years several studies have considered the potential role of the ATX/LPA axis in ovarian cancer. The high metastatic potential of ovarian carcinoma was suggested to be related to increased local production of LPA in the peritoneal cavity (Mills & Moolenaar, 2003). Levels of LPA are markedly elevated in the ascites of patients with EOC (Mills et al., 1988) and in the plasma of 90% of stage I ovarian cancer patients, compared with healthy women (Xu et al., 1998).

The outcomes of LPA-driven signalling are determined by the expression level of LPA receptors on the cell surfaces. Indeed, normal ovarian epithelial cells express low levels of mRNA for LPA2 and LPA3, whereas the mRNA levels for LPA2 and particularly LPA3, are elevated in EOC (Fang et al., 2002), suggesting a shift on ovarian cancer cells towards an LPA-dependent phenotype. Moreover >90% of LPA degradation by ovarian cancer cells is caused by the action of lipid phosphate phosphohydrolase-like (LPP-like) enzymes, whose expression differs between normal ovarian epithelium and epithelial ovarian cancer (Imai et al., 2000). This implies that LPA, its receptors and downstream metabolic cascade might be potential targets for the design of novel ovarian cancer therapies.

LPA has been found to induce VEGF expression (Hu et al., 2001) which in turn contributes to malignant ascites formation by increasing peritoneal microvessel permeability (Nagy et al., 1995). A feedback model between ATX, LPA and VEGF in ovarian cancer cells has been recently proposed (Ptaszynska et al., 2008). VEGF activates ATX transcription and subsequent protein secretion through VEGFR2. Increased secretion of ATX leads to an increased level of extracellular LPA. Completing the loop, LPA can stimulate VEGF and VEGFR2 expression through LPA receptor signalling thus enhancing tumour survival and growth. These data indicate that cross-talk between ATX and VEGF may be an important autocrine mechanism in the generation of an aggressive ovarian cancer phenotype. In addition, soluble ATX may be a beneficial target for cancer therapy because of its capacity to control both LPA production and signalling, and VEGF signalling.

The development of drug resistance to cytotoxic therapies such as carboplatin and paclitaxel as well as to newly emerging therapies (Agarwal et al., 2003), remains a high risk factor for ovarian cancer patients. Therefore, the identification of genes which confer drug resistance may offer novel therapeutic targets that can be exploited to develop drugs which re-sensitize tumour cells to chemotherapeutic agents (Richardson et al., 2005). ATX has been linked to chemoresistance due to its ability to inhibit apoptosis induced by paclitaxel in breast cancer cells (Samadi et al., 2009) and LPA can inhibit cell death induced by cisplatin (Frankel et al., 1996). It has been demonstrated that ATX may be a target for treating drug-resistant ovarian

cancer. The ectopic expression of ATX leads to the activation of a PI3K/Akt-mediated survival pathway, suggesting that ATX can delay carboplatin-induced cell death through the generation of LPA and the subsequent activation of the PI3K/Akt pathway (Vidot et al., 2010). The inhibition of ATX in therapy has the advantage of providing a single extracellular drug target capable of blocking production of LPA. It has been observed that the primary effect of ATX is to delay apoptosis induced by carboplatin; since the exposure of tumour cells to carboplatin in patients is transient, accelerating the induction of apoptosis might be beneficial and may lead to improved tumour cell destruction.

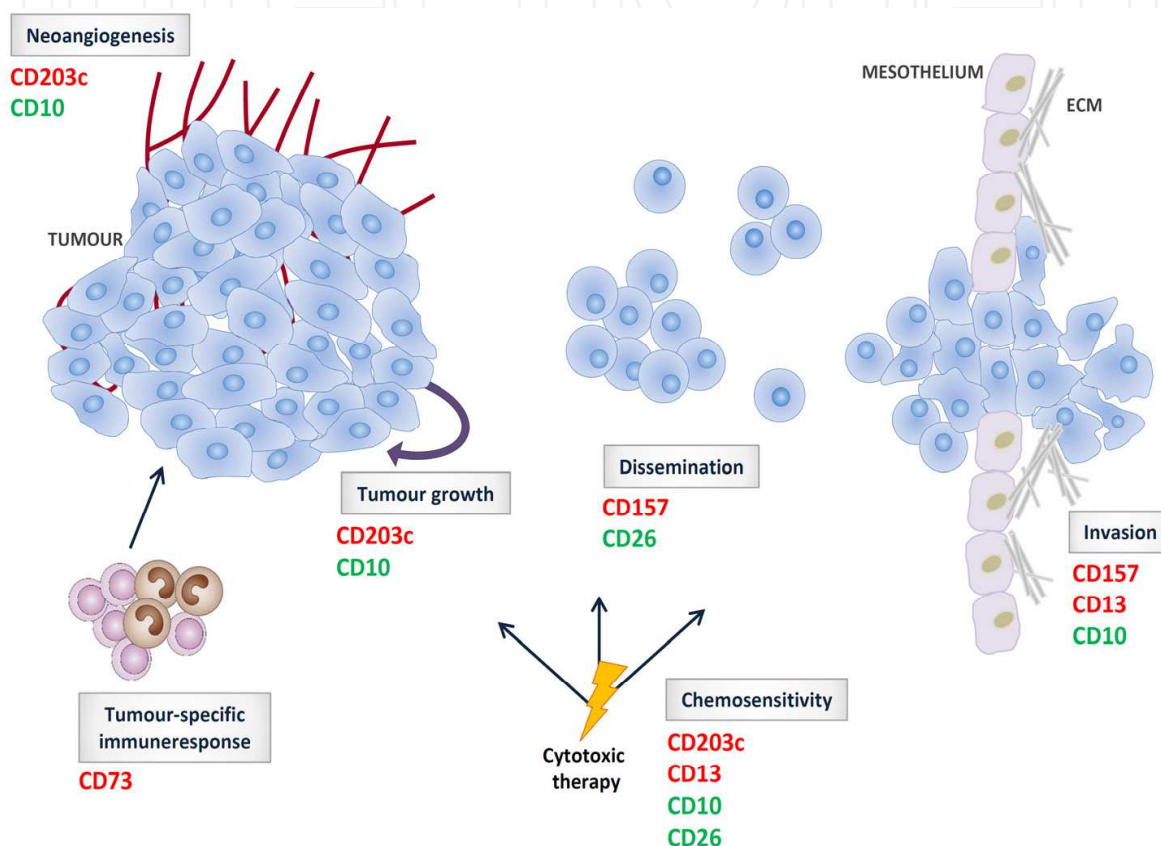


Fig. 2. Schematic representation of the role of ectoenzymes in the main steps of ovarian cancer progression. Ectoenzymes in red have stimulating effects, those in green have inhibitory effects on the indicated steps.

8. Conclusion

Improved understanding of the underlying biology of ovarian tumour progression and chemoresistance has led to the development of molecular targeted therapies. Ectoenzymes are attractive targets for designing new strategies to interfere with ovarian cancer progression and recurrence. This can be achieved by inhibiting the ectoenzymes that promote tumour migration and invasiveness (such as CD157 and CD13) or by inducing the activity of ectoenzymes that normally counteract tumour progression (such as CD26). In many cases, ectoenzymes can be inactivated either by specific monoclonal antibodies that block their function, or by small-molecule enzyme inhibitors. The dual nature of ectoenzymes warrants more detailed and vigorous investigation, because some of their

functions seem to be independent of their enzymatic activities. It is conceivable that the large extracellular domains of ectoenzymes and their lateral interaction with other membrane proteins can mediate responses without involvement of their catalytic activity. However, many of the non-substrate ligands of ectoenzymes remain to be identified. Moreover, increasing evidence indicates that a number of ectoenzymes orchestrate the immune mechanisms underlying tumour progression and outcome and it is now evident that ovarian cancer features a number of different tumour evasion mechanisms. The future challenge will be to use a combinatorial approach to increase the existing anti-tumour response, dampen tumour evasion mechanisms and target crucial environmental players.

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10. References

- Aertgeerts, K., Ye, S., Shi, L., Prasad, S. G., Witmer, D., et al. (2004) N-linked glycosylation of dipeptidyl peptidase IV (CD26): effects on enzyme activity, homodimer formation, and adenosine deaminase binding, *Protein Science*, Vol. 13 N° 1 (Jan), pp. 145-154, ISSN 0961-8368
- Agarwal, R., & Kaye, S. B. (2003) Ovarian cancer: strategies for overcoming resistance to chemotherapy, *Nature Reviews. Cancer*, Vol. 3 N° 7 (Jul), pp. 502-516, ISSN 1474-175X
- Airas, L., Salmi, M., & Jalkanen, S. (1993) Lymphocyte-vascular adhesion protein-2 is a novel 70-kDa molecule involved in lymphocyte adhesion to vascular endothelium, *Journal of Immunology*, Vol. 151 N° 8 (Oct 15), pp. 4228-4238, ISSN 0022-1767
- Airas, L. (1998) CD73 and adhesion of B-cells to follicular dendritic cells, *Leukemia and Lymphoma*, Vol. 29 N° 1-2 (Mar), pp. 37-47, ISSN 1042-8194
- Airas, L., Niemela, J., & Jalkanen, S. (2000) CD73 engagement promotes lymphocyte binding to endothelial cells via a lymphocyte function-associated antigen-1-dependent mechanism, *Journal of Immunology*, Vol. 165 N° 10 (Nov 15), pp. 5411-5417, ISSN 0022-1767
- Annunziata, C. M., & Birrer, M. J. (2010) CD157 in ovarian carcinoma: how does it help us?, *Journal of the National Cancer Institute*, Vol. 102 N° 15 (Aug 4), pp. 1104-1105, ISSN 1460-2105
- Antczak, C., De Meester, I., & Bauvois, B. (2001) Ectopeptidases in pathophysiology, *Bioessays*, Vol. 23 N° 3 (Mar), pp. 251-260, ISSN 0265-9247
- Bagnato, A., Salani, D., Di Castro, V., Wu-Wong, J. R., Tecce, R., et al. (1999) Expression of endothelin 1 and endothelin A receptor in ovarian carcinoma: evidence for an autocrine role in tumour growth, *Cancer Research*, Vol. 59 N° 3 (Feb 1), pp. 720-727, ISSN 0008-5472

- Barry, F., Boynton, R., Murphy, M., Haynesworth, S., & Zaia, J. (2001) The SH-3 and SH-4 antibodies recognize distinct epitopes on CD73 from human mesenchymal stem cells, *Biochemical and Biophysical Research Communications*, Vol. 289 N° 2 (Nov 30), pp. 519-524, ISSN 0006-291X
- Bauvois, B., De Meester, I., Dumont, J., Rouillard, D., Zhao, H. X., et al. (1999) Constitutive expression of CD26/dipeptidylpeptidase IV on peripheral blood B lymphocytes of patients with B chronic lymphocytic leukaemia, *British Journal of Cancer*, Vol. 79 N° 7-8 (Mar), pp. 1042-1048, ISSN 0007-0920
- Bhagwat, S. V., Lahdenranta, J., Giordano, R., Arap, W., Pasqualini, R., et al. (2001) CD13/APN is activated by angiogenic signals and is essential for capillary tube formation, *Blood*, Vol. 97 N° 3 (Feb 1), pp. 652-659, ISSN 0006-4971
- Black, E. J., Clair, T., Delrow, J., Neiman, P., & Gillespie, D. A. (2004) Microarray analysis identifies Autotaxin, a tumour cell motility and angiogenic factor with lysophospholipase D activity, as a specific target of cell transformation by v-Jun, *Oncogene*, Vol. 23 N° 13 (Mar 25), pp. 2357-2366, ISSN 0950-9232
- Bowes, M. A., & Kenny, A. J. (1987) An immunohistochemical study of endopeptidase-24.11 and aminopeptidase N in lymphoid tissues, *Immunology*, Vol. 60 N° 2 (Feb), pp. 247-253, ISSN 0019-2805
- Burns, D. M., Walker, B., Gray, J., & Nelson, J. (1999) Breast cancer cell-associated endopeptidase EC 24.11 modulates proliferative response to bombesin, *British Journal of Cancer*, Vol. 79 N° 2 (Jan), pp. 214-220, ISSN 0007-0920
- Cannistra, S. A. (2004) Cancer of the ovary, *New England Journal of Medicine*, Vol. 351 N° 24 (Dec 9), pp. 2519-2529, ISSN 1533-4406
- Carbone, A., Gloghini, A., Zagonel, V., Aldinucci, D., Gattei, V., et al. (1995) The expression of CD26 and CD40 ligand is mutually exclusive in human T-cell non-Hodgkin's lymphomas/leukemias, *Blood*, Vol. 86 N° 12 (Dec 15), pp. 4617-4626, ISSN 0006-4971
- Carl-McGrath, S., Lendeckel, U., Ebert, M., Wolter, A. B., Roessner, A., et al. (2004) The ectopeptidases CD10, CD13, CD26, and CD143 are upregulated in gastric cancer, *International Journal of Oncology*, Vol. 25 N° 5 (Nov), pp. 1223-1232, ISSN 1019-6439
- Carlsson, L., Ronquist, G., Eliasson, R., Egberg, N., & Larsson, A. (2006) Flow cytometric technique for determination of prostasomal quantity, size and expression of CD10, CD13, CD26 and CD59 in human seminal plasma, *International Journal of Andrology*, Vol. 29 N° 2 (Apr), pp. 331-338, ISSN 0105-6263
- Carneiro-Ramos, M. S., da Silva, V. B., Coutinho, M. B., Jr., Battastini, A. M., Sarkis, J. J., et al. (2004) Thyroid hormone stimulates 5'-ecto-nucleotidase of neonatal rat ventricular myocytes, *Molecular and Cellular Biochemistry*, Vol. 265 N° 1-2 (Oct), pp. 195-201, ISSN 0300-8177
- Chang, Y. W., Chen, S. C., Cheng, E. C., Ko, Y. P., Lin, Y. C., et al. (2005) CD13 (aminopeptidase N) can associate with tumour-associated antigen L6 and enhance the motility of human lung cancer cells, *International Journal of Cancer*, Vol. 116 N° 2 (Aug 20), pp. 243-252, ISSN 0020-7136
- Chen, L., Gao, Z., Zhu, J., & Rodgers, G. P. (2007) Identification of CD13+CD36+ cells as a common progenitor for erythroid and myeloid lineages in human bone marrow, *Experimental Hematology*, Vol. 35 N° 7 (Jul), pp. 1047-1055, ISSN 0301-472X

- Chen, M., & O'Connor, K. L. (2005) Integrin alpha6beta4 promotes expression of autotaxin/ENPP2 autocrine motility factor in breast carcinoma cells, *Oncogene*, Vol. 24 N° 32 (Jul 28), pp. 5125-5130, ISSN 0950-9232
- Cheng, H. C., Abdel-Ghany, M., & Pauli, B. U. (2003) A novel consensus motif in fibronectin mediates dipeptidyl peptidase IV adhesion and metastasis, *Journal of Biological Chemistry*, Vol. 278 N° 27 (Jul 4), pp. 24600-24607, ISSN 0021-9258
- Clayton A, Al-Taei S, Webber, D., M., Tabi, M., et al. (2011) Cancer Exosomes Express CD39 and CD73, Which Suppress T Cells through Adenosine Production, *Journal of Immunology*, Vol. 187 N° pp. 676-683
- Cohen, A. J., Bunn, P. A., Franklin, W., Magill-Solc, C., Hartmann, C., et al. (1996) Neutral endopeptidase: variable expression in human lung, inactivation in lung cancer, and modulation of peptide-induced calcium flux, *Cancer Research*, Vol. 56 N° 4 (Feb 15), pp. 831-839, ISSN 0008-5472
- Colgan, S. P., Eltzschig, H. K., Eckle, T., & Thompson, L. F. (2006) Physiological roles for ecto-5'-nucleotidase (CD73), *Purinergic Signal*, Vol. 2 N° 2 (Jun), pp. 351-360, ISSN 1573-9538
- Connelly, J. C., Skidgel, R. A., Schulz, W. W., Johnson, A. R., & Erdos, E. G. (1985) Neutral endopeptidase 24.11 in human neutrophils: cleavage of chemotactic peptide, *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 82 N° 24 (Dec), pp. 8737-8741, ISSN 0027-8424
- D'Adamio, L., Shipp, M. A., Masteller, E. L., & Reinherz, E. L. (1989) Organization of the gene encoding common acute lymphoblastic leukemia antigen (neutral endopeptidase 24.11): multiple miniexons and separate 5' untranslated regions, *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 86 N° 18 (Sep), pp. 7103-7107, ISSN 0027-8424
- Dai, J., Shen, R., Sumitomo, M., Goldberg, J. S., Geng, Y., et al. (2001) Tumour-suppressive effects of neutral endopeptidase in androgen-independent prostate cancer cells, *Clinical Cancer Research*, Vol. 7 N° 5 (May), pp. 1370-1377, ISSN 1078-0432
- Dang, N. H., Aytac, U., Sato, K., O'Brien, S., Melenhorst, J., et al. (2003) T-large granular lymphocyte lymphoproliferative disorder: expression of CD26 as a marker of clinically aggressive disease and characterization of marrow inhibition, *British Journal of Haematology*, Vol. 121 N° 6 (Jun), pp. 857-865, ISSN 0007-1048
- Danielsen, E. M., & van Deurs, B. (1997) Galectin-4 and small intestinal brush border enzymes form clusters, *Molecular Biology of the Cell*, Vol. 8 N° 11 (Nov), pp. 2241-2251, ISSN 1059-1524
- Danziger, R. S. (2008) Aminopeptidase N in arterial hypertension, *Heart Failure Reviews*, Vol. 13 N° 3 (Sep), pp. 293-298. ISSN 1382-4147
- de Micco, C., Savchenko, V., Giorgi, R., Sebag, F., & Henry, J. F. (2008) Utility of malignancy markers in fine-needle aspiration cytology of thyroid nodules: comparison of Hector Battifora mesothelial antigen-1, thyroid peroxidase and dipeptidyl aminopeptidase IV, *British Journal of Cancer*, Vol. 98 N° 4 (Feb 26), pp. 818-823, ISSN 0007-0920
- Dunphy, C. H., Gardner, L. J., Manes, J. L., Bee, C. S., & Taysi, K. (2000) CD30+ anaplastic large-cell lymphoma with aberrant expression of CD13: case report and review of the literature, *Journal of Clinical Laboratory Analysis*, Vol. 14 N° 6 pp. 299-304, ISSN 0887-8013

- Engel, M., Hoffmann, T., Wagner, L., Wermann, M., Heiser, U., et al. (2003) The crystal structure of dipeptidyl peptidase IV (CD26) reveals its functional regulation and enzymatic mechanism, *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 100 N° 9 (Apr 29), pp. 5063-5068, ISSN 0027-8424
- Erdos, E. G., & Skidgel, R. A. (1989) Neutral endopeptidase 24.11 (enkephalinase) and related regulators of peptide hormones, *FASEB Journal*, Vol. 3 N° 2 (Feb), pp. 145-151, ISSN 0892-6638
- Fang, X., Schummer, M., Mao, M., Yu, S., Tabassam, F. H., et al. (2002) Lysophosphatidic acid is a bioactive mediator in ovarian cancer, *Biochimica et Biophysica Acta*, Vol. 1582 N° 1-3 (May 23), pp. 257-264, ISSN 0006-3002
- Feki, A., Berardi, P., Bellingan, G., Major, A., Krause, K. H., et al. (2009) Dissemination of intraperitoneal ovarian cancer: Discussion of mechanisms and demonstration of lymphatic spreading in ovarian cancer model, *Critical Reviews in Oncology/Hematology*, Vol. 72 N° 1 (Oct), pp. 1-9, ISSN 1879-0461
- Ferrero, E., & Malavasi, F. (1997) Human CD38, a leukocyte receptor and ectoenzyme, is a member of a novel eukaryotic gene family of nicotinamide adenine dinucleotide+-converting enzymes: extensive structural homology with the genes for murine bone marrow stromal cell antigen 1 and aplysian ADP-ribosyl cyclase, *Journal of Immunology*, Vol. 159 N° 8 (Oct 15), pp. 3858-3865, ISSN 0022-1767
- Frankel, A., & Mills, G. B. (1996) Peptide and lipid growth factors decrease cis-diamminedichloroplatinum-induced cell death in human ovarian cancer cells, *Clinical Cancer Research*, Vol. 2 N° 8 (Aug), pp. 1307-1313, 1078-0432
- Fujii, H., Nakajima, M., Saiki, I., Yoneda, J., Azuma, I., et al. (1995) Human melanoma invasion and metastasis enhancement by high expression of aminopeptidase N/CD13, *Clinical and Experimental Metastasis*, Vol. 13 N° 5 (Sep), pp. 337-344, ISSN 0262-0898
- Fujimoto, Y., Nakanishi, Y., Sekine, S., Yoshimura, K., Akasu, T., et al. (2005) CD10 expression in colorectal carcinoma correlates with liver metastasis, *Diseases of the Colon and Rectum*, Vol. 48 N° 10 (Oct), pp. 1883-1889, ISSN 0012-3706
- Funaro, A., Ortolan, E., Ferranti, B., Gargiulo, L., Notaro, R., et al. (2004) CD157 is an important mediator of neutrophil adhesion and migration, *Blood*, Vol. 104 N° 13 (Dec 15), pp. 4269-4278, ISSN 0006-4971
- Galione, A. (1994) Cyclic ADP-ribose, the ADP-ribosyl cyclase pathway and calcium signalling, *Molecular and Cellular Endocrinology*, Vol. 98 N° 2 (Jan), pp. 125-131, ISSN 0303-7207
- Giganti, A., Rodriguez, M., Fould, B., Moulharat, N., Coge, F., et al. (2008) Murine and human autotaxin alpha, beta, and gamma isoforms: gene organization, tissue distribution, and biochemical characterization, *Journal of Biological Chemistry*, Vol. 283 N° 12 (Mar 21), pp. 7776-7789, ISSN 0021-9258
- Girardi, A. C., Degray, B. C., Nagy, T., Biemesderfer, D., & Aronson, P. S. (2001) Association of Na(+)-H(+) exchanger isoform NHE3 and dipeptidyl peptidase IV in the renal proximal tubule, *Journal of Biological Chemistry*, Vol. 276 N° 49 (Dec 7), pp. 46671-46677, ISSN 0021-9258
- Goldstein, S. C., & Todd, R. F., 3rd. (1993) Structural and biosynthetic features of the Mo5 human myeloid differentiation antigen, *Tissue Antigens*, Vol. 41 N° 4 (Apr), pp. 214-218, ISSN 0001-281

- Gorrell, M. D. (2005) Dipeptidyl peptidase IV and related enzymes in cell biology and liver disorders, *Clinical Science*, Vol. 108 N° 4 (Apr), pp. 277-292, ISSN 0143-5221
- Greaves, M. F., Hariri, G., Newman, R. A., Sutherland, D. R., Ritter, M. A., et al. (1983) Selective expression of the common acute lymphoblastic leukemia (gp 100) antigen on immature lymphoid cells and their malignant counterparts, *Blood*, Vol. 61 N° 4 (Apr), pp. 628-639, ISSN 0006-4971
- Haag, F., Adriouch, S., Brass, A., Jung, C., Moller, S., et al. (2007) Extracellular NAD and ATP: Partners in immune cell modulation, *Purinergic Signal*, Vol. 3 N° 1-2 (Mar), pp. 71-81, ISSN 1573-9546
- Hashida, H., Takabayashi, A., Kanai, M., Adachi, M., Kondo, K., et al. (2002) Aminopeptidase N is involved in cell motility and angiogenesis: its clinical significance in human colon cancer, *Gastroenterology*, Vol. 122 N° 2 (Feb), pp. 376-386, ISSN 0016-5085
- Häusler SF, Montalbán Del Barrio I, Strohschein J, Anoop Chandran P, Engel JB, et al. (2011) Ectonucleotidases CD39 and CD73 on OvCA cells are potent adenosine-generating enzymes responsible for adenosine receptor 2A-dependent suppression of T cell function and NK cell cytotoxicity. *Cancer Immunology, Immunotherapy*, Vol.60 N°10 (Oct), pp. 1405-1418, ISSN 0340-7004
- Hoelzinger, D. B., Mariani, L., Weis, J., Woyke, T., Berens, T. J., et al. (2005) Gene expression profile of glioblastoma multiforme invasive phenotype points to new therapeutic targets, *Neoplasia*, Vol. 7 N° 1 (Jan), pp. 7-16, ISSN 1522-8002
- Hoffmann-Fezer, G., Knapp, W., & Thierfelder, S. (1982) Anatomical distribution of call antigen expressing cells in normal lymphatic tissue and in lymphomas, *Leukemia Research*, Vol. 6 N° 6 pp. 761-767, ISSN 0145-2126
- Hoskin, D. W., Mader, J. S., Furlong, S. J., Conrad, D. M., & Blay, J. (2008) Inhibition of T cell and natural killer cell function by adenosine and its contribution to immune evasion by tumour cells (Review), *International Journal of Oncology*, Vol. 32 N° 3 (Mar), pp. 527-535, ISSN 1019-6439
- Hu, Y. L., Tee, M. K., Goetzl, E. J., Auersperg, N., Mills, G. B., et al. (2001) Lysophosphatidic acid induction of vascular endothelial growth factor expression in human ovarian cancer cells, *Journal of the National Cancer Institute*, Vol. 93 N° 10 (May 16), pp. 762-768, ISSN 0027-8874
- Ikeda, N., Nakajima, Y., Tokuhara, T., Hattori, N., Sho, M., et al. (2003) Clinical significance of aminopeptidase N/CD13 expression in human pancreatic carcinoma, *Clinical Cancer Research*, Vol. 9 N° 4 (Apr), pp. 1503-1508, ISSN 1078-0432
- Imai, A., Furui, T., Tamaya, T., & Mills, G. B. (2000) A gonadotropin-releasing hormone-responsive phosphatase hydrolyses lysophosphatidic acid within the plasma membrane of ovarian cancer cells, *Journal of Clinical Endocrinology and Metabolism*, Vol. 85 N° 9 (Sep), pp. 3370-3375, ISSN 0021-972X
- Ino, K., Suzuki, T., Uehara, C., Nagasaka, T., Okamoto, T., et al. (2000) The expression and localization of neutral endopeptidase 24.11/CD10 in human gestational trophoblastic diseases, *Laboratory Investigation*, Vol. 80 N° 11 (Nov), pp. 1729-1738, ISSN 0023-6837
- Ishii, K., Usui, S., Sugimura, Y., Yamamoto, H., Yoshikawa, K., et al. (2001a) Inhibition of aminopeptidase N (AP-N) and urokinase-type plasminogen activator (uPA) by zinc suppresses the invasion activity in human urological cancer cells, *Biological and Pharmaceutical Bulletin*, Vol. 24 N° 3 (Mar), pp. 226-230, ISSN 0918-6158

- Ishii, K., Usui, S., Yamamoto, H., Sugimura, Y., Tatematsu, M., et al. (2001b) Decreases of metallothionein and aminopeptidase N in renal cancer tissues, *Journal of Biochemistry*, Vol. 129 N° 2 (Feb), pp. 253-258, ISSN 0021-924X
- Jalkanen, S., & Salmi, M. (2008) VAP-1 and CD73, endothelial cell surface enzymes in leukocyte extravasation, *Arteriosclerosis, Thrombosis, and Vascular Biology*, Vol. 28 N° 1 (Jan), pp. 18-26, ISSN 1524-4636
- Jin, D., Fan, J., Wang, L., Thompson, L. F., Liu, A., et al. (2010) CD73 on tumour cells impairs antitumour T-cell responses: a novel mechanism of tumour-induced immune suppression, *Cancer Research*, Vol. 70 N° 6 (Mar 15), pp. 2245-2255, ISSN 1538-7445
- Jung, I. D., Lee, J., Lee, K. B., Park, C. G., Kim, Y. K., et al. (2004) Activation of p21-activated kinase 1 is required for lysophosphatidic acid-induced focal adhesion kinase phosphorylation and cell motility in human melanoma A2058 cells, *European Journal of Biochemistry*, Vol. 271 N° 8 (Apr), pp. 1557-1565, ISSN 0014-2956
- Kaisho, T., Ishikawa, J., Oritani, K., Inazawa, J., Tomizawa, H., et al. (1994) BST-1, a surface molecule of bone marrow stromal cell lines that facilitates pre-B-cell growth, *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 91 N° 12 (Jun 7), pp. 5325-5329, ISSN 0027-8424
- Kajiyama, H., Kikkawa, F., Suzuki, T., Shibata, K., Ino, K., et al. (2002) Prolonged survival and decreased invasive activity attributable to dipeptidyl peptidase IV overexpression in ovarian carcinoma, *Cancer Research*, Vol. 62 N° 10 (May 15), pp. 2753-2757, ISSN 0008-5472
- Kajiyama, H., Kikkawa, F., Khin, E., Shibata, K., Ino, K., et al. (2003) Dipeptidyl peptidase IV overexpression induces up-regulation of E-cadherin and tissue inhibitors of matrix metalloproteinases, resulting in decreased invasive potential in ovarian carcinoma cells, *Cancer Research*, Vol. 63 N° 9 (May 1), pp. 2278-2283, ISSN 0008-5472
- Kajiyama, H., Shibata, K., Terauchi, M., Morita, T., Ino, K., et al. (2005) Neutral endopeptidase 24.11/CD10 suppresses progressive potential in ovarian carcinoma in vitro and in vivo, *Clinical Cancer Research*, Vol. 11 N° 5 (Mar 1), pp. 1798-1808, ISSN 1078-0432
- Kajiyama, H., Shibata, K., Ino, K., Mizutani, S., Nawa, A., et al. (2010) The expression of dipeptidyl peptidase IV (DPPIV/CD26) is associated with enhanced chemosensitivity to paclitaxel in epithelial ovarian carcinoma cells, *Cancer Science*, Vol. 101 N° 2 (Feb), pp. 347-354. ISSN 1349-7006
- Kehlen, A., Lendeckel, U., Dralle, H., Langner, J., & Hoang-Vu, C. (2003) Biological significance of aminopeptidase N/CD13 in thyroid carcinomas, *Cancer Research*, Vol. 63 N° 23 (Dec 1), pp. 8500-8506. ISSN 0008-5472
- Khin, E. E., Kikkawa, F., Ino, K., Suzuki, T., Shibata, K., et al. (2003) Neutral endopeptidase/CD10 expression in the stroma of epithelial ovarian carcinoma, *International Journal of Gynecological Pathology*, Vol. 22 N° 2 (Apr), pp. 175-180, ISSN 0277-1691
- Kikkawa, F., Kajiyama, H., Shibata, K., Ino, K., Nomura, S., et al. (2005) Dipeptidyl peptidase IV in tumour progression, *Biochimica et Biophysica Acta*, Vol. 1751 N° 1 (Aug 1), pp. 45-51, ISSN 0006-3002
- Kitamura, Y., Watanabe, M., Komatsubara, S., & Sakata, Y. (1990) [Urinary excretion of glycine.prolile dipeptidile aminopeptidase, N-acetyl-beta-D-glucosaminidase, alanine aminopeptidase and low molecular protein in patients with renal cell

- carcinoma], *Hinyokika Kyo (Acta Urologica Japonica)*, Vol. 36 N° 5 (May), pp. 535-539, ISSN 0018-1994
- Knopfel, M., Davies, J. P., Duong, P. T., Kvaerno, L., Carreira, E. M., et al. (2007) Multiple plasma membrane receptors but not NPC1L1 mediate high-affinity, ezetimibe-sensitive cholesterol uptake into the intestinal brush border membrane, *Biochimica et Biophysica Acta*, Vol. 1771 N° 9 (Sep), pp. 1140-1147, ISSN 0006-3002
- Koszalka, P., Ozuyaman, B., Huo, Y., Zerneck, A., Flogel, U., et al. (2004) Targeted disruption of cd73/ecto-5'-nucleotidase alters thromboregulation and augments vascular inflammatory response, *Circulation Research*, Vol. 95 N° 8 (Oct 15), pp. 814-821, ISSN 1524-4571
- Larsen, S. L., Pedersen, L. O., Buus, S., & Stryhn, A. (1996) T cell responses affected by aminopeptidase N (CD13)-mediated trimming of major histocompatibility complex class II-bound peptides, *Journal of Experimental Medicine*, Vol. 184 N° 1 (Jul 1), pp. 183-189, ISSN 0022-1007
- Lavagno, L., Ferrero, E., Ortolan, E., Malavasi, F., & Funaro, A. (2007) CD157 is part of a supramolecular complex with CD11b/CD18 on the human neutrophil cell surface, *Journal of Biological Regulators and Homeostatic Agents*, Vol. 21 N° 1-2 pp. 5-11.
- Lee, J., Duk Jung, I., Gyo Park, C., Han, J. W., & Young Lee, H. (2006) Autotaxin stimulates urokinase-type plasminogen activator expression through phosphoinositide 3-kinase-Akt-nuclear [corrected] factor kappa B signaling cascade in human melanoma cells, *Melanoma Research*, Vol. 16 N° 5 (Oct), pp. 445-452, ISSN 0960-8931
- Lerche, C., Vogel, L. K., Shapiro, L. H., Noren, O., & Sjostrom, H. (1996) Human aminopeptidase N is encoded by 20 exons, *Mammalian Genome*, Vol. 7 N° 9 (Sep), pp. 712-713, ISSN 0938-8990
- Leth-Larsen, R., Lund, R., Hansen, H. V., Laenkholm, A. V., Tarin, D., et al. (2009) Metastasis-related plasma membrane proteins of human breast cancer cells identified by comparative quantitative mass spectrometry, *Molecular and Cellular Proteomics*, Vol. 8 N° 6 (Jun), pp. 1436-1449, ISSN 1535-9484
- Lin, M. E., Herr, D. R., & Chun, J. (2010) Lysophosphatidic acid (LPA) receptors: signaling properties and disease relevance, *Prostaglandins and Other Lipid Mediators*, Vol. 91 N° 3-4 (Apr), pp. 130-138, ISSN 1098-8823
- Liu, S., Umezugoto, M., Murph, M., Lu, Y., Liu, W., et al. (2009) Expression of autotaxin and lysophosphatidic acid receptors increases mammary tumorigenesis, invasion, and metastases, *Cancer Cell*, Vol. 15 N° 6 (Jun 2), pp. 539-550, ISSN 1878-3686
- Lo Buono, N., Parrotta, R., Morone, S., Bovino, P., Nacci, G., et al. (2011) The CD157-integrin partnership controls transendothelial migration and adhesion of human monocytes *Journal of Biological Chemistry*, Vol. 286, N°21 (May) pp. 18681-18691, ISSN 0021-9258
- Loke, S. L., Leung, C. Y., Chiu, K. Y., Yau, W. L., Cheung, K. N., et al. (1990) Localisation of CD10 to biliary canaliculi by immunoelectron microscopical examination, *Journal of Clinical Pathology*, Vol. 43 N° 8 (Aug), pp. 654-656, ISSN 0021-9746
- Madara, J. L., Patapoff, T. W., Gillice-Castro, B., Colgan, S. P., Parkos, C. A., et al. (1993) 5'-adenosine monophosphate is the neutrophil-derived paracrine factor that elicits chloride secretion from T84 intestinal epithelial cell monolayers, *Journal of Clinical Investigation*, Vol. 91 N° 5 (May), pp. 2320-2325, ISSN 0021-9738

- Maienschein, V., & Zimmermann, H. (1996) Immunocytochemical localization of ecto-5'-nucleotidase in cultures of cerebellar granule cells, *Neuroscience*, Vol. 70 N° 2 (Jan), pp. 429-438, ISSN 0306-4522
- Malavasi, F., Deaglio, S., Funaro, A., Ferrero, E., Horenstein, A. L., et al. (2008) Evolution and function of the ADP ribosyl cyclase/CD38 gene family in physiology and pathology, *Physiological Reviews*, Vol. 88 N° 3 (Jul), pp. 841-886, ISSN 0031-9333
- Massaia, M., Pileri, A., Boccadoro, M., Bianchi, A., Palumbo, A., et al. (1988) The generation of alloreactive cytotoxic T lymphocytes requires the expression of ecto-5'nucleotidase activity, *Journal of Immunology*, Vol. 141 N° 11 (Dec 1), pp. 3768-3775, ISSN 0022-1767
- Masuda, A., Nakamura, K., Izutsu, K., Igarashi, K., Ohkawa, R., et al. (2008) Serum autotaxin measurement in haematological malignancies: a promising marker for follicular lymphoma, *British Journal of Haematology*, Vol. 143 N° 1 (Oct), pp. 60-70, ISSN 1365-2141
- Matsas, R., Stephenson, S. L., Hryszko, J., Kenny, A. J., & Turner, A. J. (1985) The metabolism of neuropeptides. Phase separation of synaptic membrane preparations with Triton X-114 reveals the presence of aminopeptidase N, *Biochemical Journal*, Vol. 231 N° 2 (Oct 15), pp. 445-449, ISSN 0264-6021
- Metzgar, R. S., Borowitz, M. J., Jones, N. H., & Dowell, B. L. (1981) Distribution of common acute lymphoblastic leukemia antigen in nonhematopoietic tissues, *Journal of Experimental Medicine*, Vol. 154 N° 4 (Oct 1), pp. 1249-1254, ISSN 0022-1007
- Miki, T., Takegami, Y., Okawa, K., Muraguchi, T., Noda, M., et al. (2007) The reversion-inducing cysteine-rich protein with Kazal motifs (RECK) interacts with membrane type 1 matrix metalloproteinase and CD13/aminopeptidase N and modulates their endocytic pathways, *Journal of Biological Chemistry*, Vol. 282 N° 16 (Apr 20), pp. 12341-12352, ISSN 0021-9258
- Mills, G. B., May, C., McGill, M., Roifman, C. M., & Mellors, A. (1988) A putative new growth factor in ascitic fluid from ovarian cancer patients: identification, characterization, and mechanism of action, *Cancer Research*, Vol. 48 N° 5 (Mar 1), pp. 1066-1071, ISSN 0008-5472
- Mills, G. B., & Moolenaar, W. H. (2003) The emerging role of lysophosphatidic acid in cancer, *Nature Reviews. Cancer*, Vol. 3 N° 8 (Aug), pp. 582-591. 1474-175X
- Mina-Osorio, P., & Ortega, E. (2005) Aminopeptidase N (CD13) functionally interacts with FcγR3 in human monocytes, *Journal of Leukocyte Biology*, Vol. 77 N° 6 (Jun), pp. 1008-1017, ISSN 0741-5400
- Mina-Osorio, P., Shapiro, L. H., & Ortega, E. (2006) CD13 in cell adhesion: aminopeptidase N (CD13) mediates homotypic aggregation of monocytic cells, *Journal of Leukocyte Biology*, Vol. 79 N° 4 (Apr), pp. 719-730, ISSN 0741-5400
- Mizutani, S., Kajiyama, H., Suzuki, T., Shibata, K., Ino, K., et al. (2003) Survival time and invasive activity due to dipeptidyl peptidase IV overexpression in ovarian carcinoma, *Advances in Experimental Medicine and Biology*, Vol. 524 N° pp. 253-256, ISSN 0065-2598
- Moreschi, I., Bruzzone, S., Bodrato, N., Usai, C., Guida, L., et al. (2008) NAADP⁺ is an agonist of the human P2Y₁₁ purinergic receptor, *Cell Calcium*, Vol. 43 N° 4 (Apr), pp. 344-355, ISSN 0143-4160

- Morrison, M. E., Vijayasaradhi, S., Engelstein, D., Albino, A. P., & Houghton, A. N. (1993) A marker for neoplastic progression of human melanocytes is a cell surface ectopeptidase, *Journal of Experimental Medicine*, Vol. 177 N° 4 (Apr 1), pp. 1135-1143, ISSN 0022-1007
- Muraoka, O., Tanaka, H., Itoh, M., Ishihara, K., & Hirano, T. (1996) Genomic structure of human BST-1, *Immunology Letters*, Vol. 54 N° 1 (Dec 1), pp. 1-4, ISSN 0165-2478
- Nagy, J. A., Masse, E. M., Herzberg, K. T., Meyers, M. S., Yeo, K. T., et al. (1995) Pathogenesis of ascites tumour growth: vascular permeability factor, vascular hyperpermeability, and ascites fluid accumulation, *Cancer Research*, Vol. 55 N° 2 (Jan 15), pp. 360-368, ISSN 0008-5472
- Nakai, Y., Ikeda, H., Nakamura, K., Kume, Y., Fujishiro, M., et al. (2011) Specific increase in serum autotaxin activity in patients with pancreatic cancer, *Clinical Biochemistry*, Vol. 44 N° 8-9 (Jun), pp. 576-581, ISSN 1873-2933
- Nakanaga, K., Hama, K., & Aoki, J. (2010) Autotaxin--an LPA producing enzyme with diverse functions, *J Biochem*, Vol. 148 N° 1 (Jul), pp. 13-24, ISSN 1756-2651
- Nam, S. W., Clair, T., Campo, C. K., Lee, H. Y., Liotta, L. A., et al. (2000) Autotaxin (ATX), a potent tumour motogen, augments invasive and metastatic potential of ras-transformed cells, *Oncogene*, Vol. 19 N° 2 (Jan 13), pp. 241-247, ISSN 0950-9232
- Nam, S. W., Clair, T., Kim, Y. S., McMarlin, A., Schiffmann, E., et al. (2001) Autotaxin (NPP-2), a metastasis-enhancing motogen, is an angiogenic factor, *Cancer Research*, Vol. 61 N° 18 (Sep 15), pp. 6938-6944, ISSN 0008-5472
- Naora, H., & Montell, D. J. (2005) Ovarian cancer metastasis: integrating insights from disparate model organisms, *Nature Reviews. Cancer*, Vol. 5 N° 5 (May), pp. 355-366, ISSN 1474-175X
- Nemoto, E., Kunii, R., Tada, H., Tsubahara, T., Ishihata, H., et al. (2004) Expression of CD73/ecto-5'-nucleotidase on human gingival fibroblasts and contribution to the inhibition of interleukin-1 α -induced granulocyte-macrophage colony stimulating factor production, *Journal of Periodontal Research*, Vol. 39 N° 1 (Feb), pp. 10-19, ISSN 0022-3484
- Nishimasu, H., Okudaira, S., Hama, K., Mihara, E., Dohmae, N., et al. (2011) Crystal structure of autotaxin and insight into GPCR activation by lipid mediators, *Nature Structural and Molecular Biology*, Vol. 18 N° 2 (Feb), pp. 205-212, ISSN 1545-9985
- Noble, F., & Roques, B. P. (1997) Association of aminopeptidase N and endopeptidase 24.15 inhibitors potentiate behavioral effects mediated by nociceptin/orphanin FQ in mice, *FEBS Letters*, Vol. 401 N° 2-3 (Jan 20), pp. 227-229, ISSN 0014-5793
- Nomura, R., Kiyota, A., Suzaki, E., Kataoka, K., Ohe, Y., et al. (2004) Human coronavirus 229E binds to CD13 in rafts and enters the cell through caveolae, *Journal of Virology*, Vol. 78 N° 16 (Aug), pp. 8701-8708, ISSN 0022-538X
- Noren, O. (1986) The enzymes of the enterocyte plasma membrane, In: *Molecular and cellular basis of digestion*, Desnuelle P., 133-167, Elsevier, Amsterdam, Holland.
- O'Hare, M. J., Ormerod, M. G., Monaghan, P., Lane, E. B., & Gusterson, B. A. (1991) Characterization in vitro of luminal and myoepithelial cells isolated from the human mammary gland by cell sorting, *Differentiation*, Vol. 46 N° 3 (Apr), pp. 209-221, ISSN 0301-4681
- Ohta, A., Gorelik, E., Prasad, S. J., Ronchese, F., Lukashev, D., et al. (2006) A2A adenosine receptor protects tumours from antitumour T cells, *Proceedings of the National*

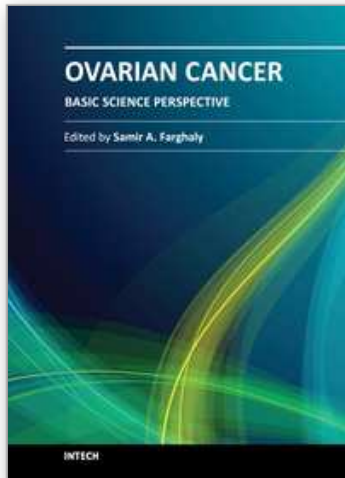
- Academy of Sciences of the United States of America*, Vol. 103 N° 35 (Aug 29), pp. 13132-13137, ISSN 0027-8424
- Olsen, J., Cowell, G. M., Konigshofer, E., Danielsen, E. M., Moller, J., et al. (1988) Complete amino acid sequence of human intestinal aminopeptidase N as deduced from cloned cDNA, *FEBS Letters*, Vol. 238 N° 2 (Oct 10), pp. 307-314, ISSN 0014-5793
- Ortolan, E., Vacca, P., Capobianco, A., Armando, E., Crivellin, F., et al. (2002) CD157, the Janus of CD38 but with a unique personality, *Cell Biochemistry and Function*, Vol. 20 N° 4 (Dec), pp. 309-322, ISSN 0263-6484
- Ortolan, E., Tibaldi, E. V., Ferranti, B., Lavagno, L., Garbarino, G., et al. (2006) CD157 plays a pivotal role in neutrophil transendothelial migration, *Blood*, Vol. 108 N° 13 (Dec 15), pp. 4214-4222, ISSN 0006-4971
- Ortolan, E., Arisio, R., Morone, S., Bovino, P., Lo-Buono, N., et al. (2010) Functional Role and Prognostic Significance of CD157 in Ovarian Carcinoma, *Journal of the National Cancer Institute*, Vol. 105 N° 16 (Jul 16), pp. 1160-1177, ISSN 1460-2105
- Papandreou, C. N., Usmani, B., Geng, Y., Bogenrieder, T., Freeman, R., et al. (1998) Neutral endopeptidase 24.11 loss in metastatic human prostate cancer contributes to androgen-independent progression, *Nature Medicine*, Vol. 4 N° 1 (Jan), pp. 50-57, ISSN 1078-8956
- Pesando, J. M., Tomaselli, K. J., Lazarus, H., & Schlossman, S. F. (1983) Distribution and modulation of a human leukemia-associated antigen (CALLA), *Journal of Immunology*, Vol. 131 N° 4 (Oct), pp. 2038-2045, ISSN 0022-1767
- Pethiyagoda, C. L., Welch, D. R., & Fleming, T. P. (2000) Dipeptidyl peptidase IV (DPPIV) inhibits cellular invasion of melanoma cells, *Clinical and Experimental Metastasis*, Vol. 18 N° 5 pp. 391-400, ISSN 0262-0898
- Pfleiderer, G., & Celliers, P. G. (1963) [Isolation of an Aminopeptidase from Kidney Particles], *Biochemische Zeitschrift*, Vol. 339 N° (Dec 3), pp. 186-189. ISSN 0366-0753
- Ptaszynska, M. M., Pendrak, M. L., Bandle, R. W., Stracke, M. L., & Roberts, D. D. (2008) Positive feedback between vascular endothelial growth factor-A and autotaxin in ovarian cancer cells, *Molecular Cancer Research*, Vol. 6 N° 3 (Mar), pp. 352-363, ISSN 1541-7786
- Rabinovich, G. A., Gabrilovich, D., & Sotomayor, E. M. (2007) Immunosuppressive strategies that are mediated by tumour cells, *Annual Review of Immunology*, Vol. 25 N° pp. 267-296, ISSN 0732-0582
- Razak, K., & Newland, A. C. (1992) The significance of aminopeptidases and haematopoietic cell differentiation, *Blood Reviews*, Vol. 6 N° 4 (Dec), pp. 243-250, ISSN 0268-960X
- Resta, R., Yamashita, Y., & Thompson, L. F. (1998) Ecto-enzyme and signaling functions of lymphocyte CD73, *Immunological Reviews*, Vol. 161 N° (Feb), pp. 95-109, ISSN 0105-2896
- Richardson, A., & Kaye, S. B. (2005) Drug resistance in ovarian cancer: the emerging importance of gene transcription and spatio-temporal regulation of resistance, *Drug Resistance Updates*, Vol. 8 N° 5 (Oct), pp. 311-321, ISSN 1368-7646
- Ritz, J., Pesando, J. M., Notis-McConarty, J., Lazarus, H., & Schlossman, S. F. (1980) A monoclonal antibody to human acute lymphoblastic leukaemia antigen, *Nature*, Vol. 283 N° 5747 (Feb 7), pp. 583-585, ISSN 0028-0836

- Ross, J. A., Ansell, I., Hjelle, J. T., Anderson, J. D., Miller-Hjelle, M. A., et al. (1998) Phenotypic mapping of human mesothelial cells, *Advances in Peritoneal Dialysis*, Vol. 14 N° pp. 25-30, ISSN 1197-8554
- Saiki, I., Fujii, H., Yoneda, J., Abe, F., Nakajima, M., et al. (1993) Role of aminopeptidase N (CD13) in tumour-cell invasion and extracellular matrix degradation, *International Journal of Cancer*, Vol. 54 N° 1 (Apr 22), pp. 137-143, ISSN 0020-7136
- Salani, D., Di Castro, V., Nicotra, M. R., Rosano, L., Tecce, R., et al. (2000) Role of endothelin-1 in neovascularization of ovarian carcinoma, *American Journal of Pathology*, Vol. 157 N° 5 (Nov), pp. 1537-1547, ISSN 0002-9440
- Salles, G., Chen, C. Y., Reinherz, E. L., & Shipp, M. A. (1992) CD10/NEP is expressed on Thy-1low B220+ murine B-cell progenitors and functions to regulate stromal cell-dependent lymphopoiesis, *Blood*, Vol. 80 N° 8 (Oct 15), pp. 2021-2029, ISSN 0006-4971
- Salmi, M., & Jalkanen, S. (2011) Homing-associated molecules CD73 and VAP-1 as targets to prevent harmful inflammations and cancer spread, *FEBS Letters*, Vol. 585 N° 11 (Jun 6), pp. 1543-1550, ISSN 1873-3468
- Samadi, N., Gaetano, C., Goping, I. S., & Brindley, D. N. (2009) Autotaxin protects MCF-7 breast cancer and MDA-MB-435 melanoma cells against Taxol-induced apoptosis, *Oncogene*, Vol. 28 N° 7 (Feb 19), pp. 1028-1039, ISSN 1476-5594
- Samadi, N., Bekele, R. T., Goping, I. S., Schang, L. M., & Brindley, D. N. (2011) Lysophosphatidate induces chemo-resistance by releasing breast cancer cells from taxol-induced mitotic arrest, *PLoS ONE*, Vol. 6 N° 5 pp. e20608, ISSN 1932-6203
- Santos, A. N., Langner, J., Herrmann, M., & Riemann, D. (2000) Aminopeptidase N/CD13 is directly linked to signal transduction pathways in monocytes, *Cellular Immunology*, Vol. 201 N° 1 (Apr 10), pp. 22-32, ISSN 0008-8749
- Semenza, G. (1986) Anchoring and biosynthesis of stalked brush border membrane proteins: glycosidases and peptidases of enterocytes and renal tubuli, *Annual Review of Cell Biology*, Vol. 2 N° pp. 255-313, ISSN 0743-4634
- Shipp, M. A., Richardson, N. E., Sayre, P. H., Brown, N. R., Masteller, E. L., et al. (1988) Molecular cloning of the common acute lymphoblastic leukemia antigen (CALLA) identifies a type II integral membrane protein, *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 85 N° 13 (Jul), pp. 4819-4823, ISSN 0027-8424
- Shipp, M. A., Vijayaraghavan, J., Schmidt, E. V., Masteller, E. L., D'Adamio, L., et al. (1989) Common acute lymphoblastic leukemia antigen (CALLA) is active neutral endopeptidase 24.11 ("enkephalinase"): direct evidence by cDNA transfection analysis, *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 86 N° 1 (Jan), pp. 297-301, ISSN 0027-8424
- Shipp, M. A., & Look, A. T. (1993) Hematopoietic differentiation antigens that are membrane-associated enzymes: cutting is the key!, *Blood*, Vol. 82 N° 4 (Aug 15), pp. 1052-1070, ISSN 0006-4971
- Spychala, J., Lazarowski, E., Ostapkowicz, A., Ayscue, L. H., Jin, A., et al. (2004) Role of estrogen receptor in the regulation of ecto-5'-nucleotidase and adenosine in breast cancer, *Clinical Cancer Research*, Vol. 10 N° 2 (Jan 15), pp. 708-717, ISSN 1078-0432
- Stagg, J., Divisekera, U., McLaughlin, N., Sharkey, J., Pommey, S., et al. (2010a) Anti-CD73 antibody therapy inhibits breast tumour growth and metastasis, *Proceedings of the*

- National Academy of Sciences of the United States of America*, Vol. 107 N° 4 (Jan 26), pp. 1547-1552, ISSN 1091-6490
- Stagg, J., & Smyth, M. J. (2010b) Extracellular adenosine triphosphate and adenosine in cancer, *Oncogene*, Vol. 29 N° 39 (Sep 30), pp. 5346-5358, ISSN 1476-5594
- Stracke, M. L., Krutzsch, H. C., Unsworth, E. J., Arestad, A., Cioce, V., et al. (1992) Identification, purification, and partial sequence analysis of autotaxin, a novel motility-stimulating protein, *Journal of Biological Chemistry*, Vol. 267 N° 4 (Feb 5), pp. 2524-2529, ISSN 0021-9258
- Stremenova, J., Krepela, E., Mares, V., Trim, J., Dbaly, V., et al. (2007) Expression and enzymatic activity of dipeptidyl peptidase-IV in human astrocytic tumours are associated with tumour grade, *International Journal of Oncology*, Vol. 31 N° 4 (Oct), pp. 785-792, ISSN 1019-6439
- Strohmeier, G. R., Lencer, W. I., Patapoff, T. W., Thompson, L. F., Carlson, S. L., et al. (1997) Surface expression, polarization, and functional significance of CD73 in human intestinal epithelia, *Journal of Clinical Investigation*, Vol. 99 N° 11 (Jun 1), pp. 2588-2601, ISSN 0021-9738
- Suzuki, T., Kikkawa, F., Ino, K., Nagasaka, T., Tamakoshi, K., et al. (2001) Imbalance between neutral endopeptidase 24.11 and endothelin-1 expression in human endometrial carcinoma, *Oncology*, Vol. 60 N° 3 pp. 258-267, ISSN 0030-2414
- Tanaka, T., Camerini, D., Seed, B., Torimoto, Y., Dang, N. H., et al. (1992) Cloning and functional expression of the T cell activation antigen CD26, *Journal of Immunology*, Vol. 149 N° 2 (Jul 15), pp. 481-486, ISSN 0022-1767
- ten Kate, J., Wijnen, J. T., van der Goes, R. G., Quadt, R., Griffioen, G., et al. (1984) Quantitative changes in adenosine deaminase isoenzymes in human colorectal adenocarcinomas, *Cancer Research*, Vol. 44 N° 10 (Oct), pp. 4688-4692, ISSN 0008-5472
- Terauchi, M., Kajiyama, H., Shibata, K., Ino, K., Nawa, A., et al. (2007) Inhibition of APN/CD13 leads to suppressed progressive potential in ovarian carcinoma cells, *BMC Cancer*, Vol. 7 N° pp. 140, ISSN 1471-2407
- Tokumura, A., Majima, E., Kariya, Y., Tominaga, K., Kogure, K., et al. (2002) Identification of human plasma lysophospholipase D, a lysophosphatidic acid-producing enzyme, as autotaxin, a multifunctional phosphodiesterase, *Journal of Biological Chemistry*, Vol. 277 N° 42 (Oct 18), pp. 39436-39442, ISSN 0021-9258
- van Hensbergen, Y., Broxterman, H. J., Hanemaaijer, R., Jorna, A. S., van Lent, N. A., et al. (2002) Soluble aminopeptidase N/CD13 in malignant and nonmalignant effusions and intratumoural fluid, *Clinical Cancer Research*, Vol. 8 N° 12 (Dec), pp. 3747-3754, ISSN 1078-0432
- van Hensbergen, Y., Broxterman, H. J., Rana, S., van Diest, P. J., Duyndam, M. C., et al. (2004) Reduced growth, increased vascular area, and reduced response to cisplatin in CD13-overexpressing human ovarian cancer xenografts, *Clinical Cancer Research*, Vol. 10 N° 3 (Feb 1), pp. 1180-1191, ISSN 1078-0432
- van Meeteren, L. A., & Moolenaar, W. H. (2007) Regulation and biological activities of the autotaxin-LPA axis, *Progress in Lipid Research*, Vol. 46 N° 2 (Mar), pp. 145-160, ISSN 0163-7827

- Vidot, S., Witham, J., Agarwal, R., Greenhough, S., Bamrah, H. S., et al. (2010) Autotaxin delays apoptosis induced by carboplatin in ovarian cancer cells, *Cellular Signalling*, Vol. 22 N° 6 (Jun), pp. 926-935, ISSN 1873-3913
- Watanabe, N., Ikeda, H., Nakamura, K., Ohkawa, R., Kume, Y., et al. (2007) Both plasma lysophosphatidic acid and serum autotaxin levels are increased in chronic hepatitis C, *Journal of Clinical Gastroenterology*, Vol. 41 N° 6 (Jul), pp. 616-623, ISSN 0192-0790
- Wesley, U. V., Albino, A. P., Tiwari, S., & Houghton, A. N. (1999) A role for dipeptidyl peptidase IV in suppressing the malignant phenotype of melanocytic cells, *Journal of Experimental Medicine*, Vol. 190 N° 3 (Aug 2), pp. 311-322, ISSN 0022-1007
- Xu, Y., Shen, Z., Wiper, D. W., Wu, M., Morton, R. E., et al. (1998) Lysophosphatidic acid as a potential biomarker for ovarian and other gynecologic cancers, *JAMA*, Vol. 280 N° 8 (Aug 26), pp. 719-723, ISSN 0098-7484
- Yamaguchi, U., Nakayama, R., Honda, K., Ichikawa, H., Hasegawa, T., et al. (2008) Distinct gene expression-defined classes of gastrointestinal stromal tumour, *Journal of Clinical Oncology*, Vol. 26 N° 25 (Sep 1), pp. 4100-4108, ISSN 1527-7755
- Yamashita, M., Kajiyama, H., Terauchi, M., Shibata, K., Ino, K., et al. (2007) Involvement of aminopeptidase N in enhanced chemosensitivity to paclitaxel in ovarian carcinoma in vitro and in vivo, *International Journal of Cancer*, Vol. 120 N° 10 (May 15), pp. 2243-2250, ISSN 0020-7136
- Zhang, B. (2010) CD73: a novel target for cancer immunotherapy, *Cancer Research*, Vol. 70 N° 16 (Aug 15), pp. 6407-6411, ISSN 1538-7445
- Zhang, M. Z., Qiao, Y. H., & Suo, Z. H. (2008) [Correlation of DPPIV expression with clinicopathological features and prognosis in epithelial ovarian carcinoma], *Zhonghua Zhong Liu Za Zhi (Chinese Journal of Oncology)*, Vol. 30 N° 11 (Nov), pp. 848-852, ISSN 0253-3766
- Zhao, H., Ramos, C. F., Brooks, J. D., & Peehl, D. M. (2007) Distinctive gene expression of prostatic stromal cells cultured from diseased versus normal tissues, *Journal of Cellular Physiology*, Vol. 210 N° 1 (Jan), pp. 111-121, ISSN 0021-9541

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Worldwide, Ovarian carcinoma continues to be responsible for more deaths than all other gynecologic malignancies combined. International leaders in the field address the critical biologic and basic science issues relevant to the disease. The book details the molecular biological aspects of ovarian cancer. It provides molecular biology techniques of understanding this cancer. The techniques are designed to determine tumor genetics, expression, and protein function, and to elucidate the genetic mechanisms by which gene and immunotherapies may be perfected. It provides an analysis of current research into aspects of malignant transformation, growth control, and metastasis. A comprehensive spectrum of topics is covered providing up to date information on scientific discoveries and management considerations.

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