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Review

CD138 (syndecan-1) expression in health and disease

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Summary. CD138 (syndecan-1, Sdc-1) is a member of the syndecan family that comprises heparan sulfate proteoglycans. CD138 is significant for cell-cell and cell-matrix interactions. In adult human tissues, CD138 is predominantly expressed in epithelial cells and plasmacytes. CD138 immunoexpression is altered in a wide spectrum of benign inflammatory, infectious and fibrotic diseases (colitis, allergic contact dermatitis, fibrosis of various organs, etc) and diabetes mellitus type II. Furthermore, CD138 is involved in molecular pathways that are deregulated during carcinogenesis and are related to cell proliferation, apoptosis, angiogenesis, tumour invasion and metastasis. CD138 tumour cell and stromal immunoexpression is modified in various types of cancer, and is frequently correlated with clinico-pathological parameters and patients' prognosis. The soluble form of CD138 may be used as a prognostic serum biomarker with promising results in respiratory tract carcinomas. CD138 plays a crucial role in carcinogenesis and is an attractive target for anticancer treatment with heparanase inhibitors and anti-CD138 antibodies for immunotherapy.

Key words: CD138, Syndecan-1, Carcinoma, Metastasis, Prognosis

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Introduction

CD138 (syndecan-1, Sdc-1) belongs to the family of syndecans, which are transmembrane heparan sulfate proteoglycans-HSPG). The word "syndecan" derives from the Greek word "syndein", which means "to bind together", and thus reflects its biological role. Syndecans regulate cell-cell and cell-matrix interactions. The mammalian syndecan family consists of four members, each encoded by distinct genes. All cell types, except erythrocytes, express at least one member of the syndecan family. In adult tissues, CD138 is predominantly expressed by epithelial cells and plasmacytes (Fears and Woods, 2006; Manon-Jensen et al., 2010; Teng et al., 2012)

This review will provide an overview of: 1) key molecular pathways in which CD138 is involved and which are disrupted during carcinogenesis, 2) the role of CD138 in non-neoplastic diseases, and 3) the immunohistochemical expression of CD138 in human carcinomas in relation to clinico-pathological parameters and patients' survival.

1. CD138 molecular structure

All members of the syndecan family have common structural characteristics. Three structural domains are recognized: extracellular (ectodomain-ED), trans-membrane (TM) and cytoplasmic (CM) domain (Fig. 1).

The ED is unique for each syndecan and is composed by heparan sulfate (HS) chains attached distally to the plasma membrane. The N-terminal ED has glycosaminoglycan (GAG) chain substitution sites.

These are predominantly HS covalently linked to serine residues in a serine-glycine motif surrounded by acidic residues. HS may be substituted by chondroitin or dermatan sulfate at sites closer to the transmembrane domain (Manon-Jensen et al., 2010).

The transmembrane domain contains a GxxxG dimerization motif and mediates both homotypic and heterotypic dimerization of syndecans (Dews and Mackenzie, 2007)

The cytoplasmic domain consists of a membrane-proximal C1 and distal C2 conserved region flanking a variable region (V) that is unique to each syndecan, and conserved across species. Moreover, the cytoplasmic domain contains several conserved signaling and scaffolding motifs, like the PDZ [post synaptic density protein (PSD95), Drosophila disc large tumour suppressor (Dlg1), and Zonula occludens-1 protein (zo-1)] binding domain at the C terminus (Manon-Jensen et al., 2010). PDZ interactions are important for cell polarization (Lambaerts et al., 2009).

All syndecans interact with various ligands (soluble factors, cell associated molecules and extracellular matrix components) with either one of the three domains (ED, TM, CM) and regulate their biological activity by affecting ligand stability, conformation, oligomerization, or compartmentalization (Lambaerts et al., 2009; Teng et al., 2012).

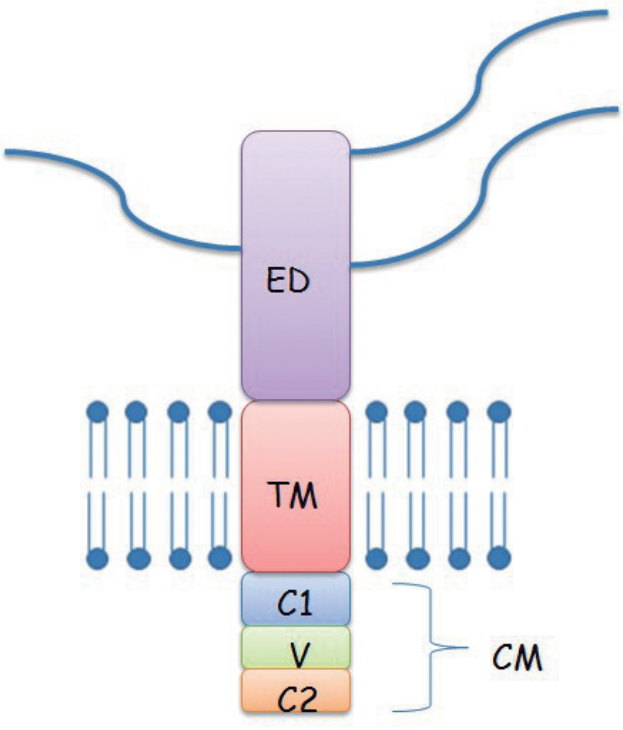

Fig. 1. CD138 molecular structure. All members of the syndecan family have common structural characteristics. Three structural domains are recognized: extracellular (ectodomain-ED), transmembrane (TM) (crossing the double phospholipid layer of the cell membrane shown in blue) and cytoplasmic (CM) domain.

1.1 Ectodomain shedding

All syndecans, including CD138, undergo regulated proteolytic cleavage, usually near the cell membrane, in a process known as shedding. CD138 HS chains are cleaved at specific sites by heparanase, producing fragments of 10-20 sugar units (Lambaerts et al., 2009). Moreover, specific enzymes called sheddases may proteolytically cleave the ED. This cleavage leads to the reduction of HS chains, and to the production of shed EDs (soluble syndecans), which can act as effectors with autocrine or paracrine action. Syndecans can regulate the biological activity of ligands by affecting their stability, conformation, oligomerization, or compartmentalization (Teng et al., 2012). ED shedding may lead to: 1) downregulation of specific molecular pathways, as the part of CD138 that remains after shedding is not able to interact with ligands, and 2) conversion of the membrane bound receptors to soluble effectors or antagonists. In the cell microenvironment, shed EDs compete with those that remain unshed, for ligand attachment.

Shedding is a process which is strictly regulated and its dysregulation characterises diseases like cancer (Teng et al., 2012). Cleavage of HS chains by heparanase, enhances shedding because the absence of HS chains facilitates approaching of sheddases to EDs (Lambaerts et al., 2009). EDs can be shed by matrix metallo-proteinase (MMP)-7 (Ding et al., 2005), MMP-2, MMP-9 (Brule et al., 2006), membrane associated metalloproteinases MT1-MMP, MT3-MMP (Endo et al., 2003), as well as ADAM17 (TACE) (disintegrin and metalloproteinase domain protein 17- tumor necrosis a converting enzyme) (Pruessmeyer et al., 2010). ED shedding is induced by growth factors, chemokines, bacterial toxins and oxidative stress (Teng et al., 2012).

1.2 CD138 in non neoplastic diseases

1.2.1 CD138 in inflammatory diseases.

CD138 binds to ligands that regulate the process of inflammation. The role of CD138 in various inflammatory diseases has been studied *in vivo and in vitro*. CD138 is involved in leucocyte recruitment, generation of chemokine gradient, and in extracellular matrix remodeling during restoration of normal structure and function of injured tissues. Various experiments in cell lines and animal models have shown that dysregulation of syndecan shedding is implicated in allergic contact dermatitis, allergic lung inflammation, dextran sodium sulfate-induced colitis, idiopathic pulmonary fibrosis, antiglomerulal basement membrane nephritis, cardiac fibrosis, protein-losing enteropathy, and myocardial infarction (Teng et al., 2012). CD138 is implicated in the maintenance of intestinal barrier function in normal intestine. Recently, it has been reported that CD138 protein expression levels are

decreased in colonic mucosa and increased in the serum of patients with Crohn's disease compared to patients with functional bowel disorders or intestinal tuberculosis (Zhang et al., 2013).

1.2.2 CD138 and infectious diseases

CD138 is the main HPSG of endothelial cells and plays a crucial role in microbial inflection, especially during its early phase. It may act as receptor for binding of various pathogens (viruses, bacteria, parasites). Several studies suggest that CD138 is involved in the initial attachment and subsequent entry of pathogens into host cells and the inhibition of host immune response. CD138 is implicated in Hepatitis E virus, Human papilloma virus, Herpes simplex virus and Human immunodeficiency virus infections (Teng et al., 2012). The cytoplasmic domain of CD138 participates in *Neisseria gonorrhoeae* infection. Bacteria like *Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae* and *Bacillus anthracis* have been shown to induce CD138 ED shedding (Teng et al., 2012).

1.2.3 CD138 and other benign human diseases

CD138 may play important role in obesity as it binds to ARG (Aguti Related Protein), which is implicated in stimulation of food consumption (Fears and Woods, 2006). Many studies connect CD138 with pathogenesis of diabetes mellitus (Teng et al., 2012). Elevated sCD138 serum levels have been detected in diabetic patients, while their neutrophils overexpress CD138 (Wang et al., 2012). CD138 placental overexpression is a predictive fetal factor for pregnancy outcome (Schmedt et al., 2012). Finally, patients that suffer from active systemic lupus erythematosus have increased serum concentration of sCD138 (Minowa et al., 2011).

2. CD138 and molecular pathways implicated in carcinogenesis

The role of CD138 is of paramount importance during carcinogenesis as it is involved in the dysregulation of pathways that control cell proliferation, apoptosis, angiogenesis, and cell anchorage.

2.1 CD138, cell proliferation and apoptosis

2.1.a Cell proliferation

The most fundamental trait of cancer cells involves their ability to sustain chronic proliferation. Normal tissues strictly govern the production and release of growth-promoting signals, in order to control cell proliferation and apoptosis, and consequently ensure the maintenance of normal tissue structure and function. Cancer cells by “deregulating these signals, become masters of their own destinies” (Hanahan and Weinberg 2011).

Evidence supports the implication of CD138 in the WNT signal transduction pathway. Transgenic mice that did not express CD138 (CD138-/-) were protected from WNT induced carcinogenesis (Alexander et al., 2000).

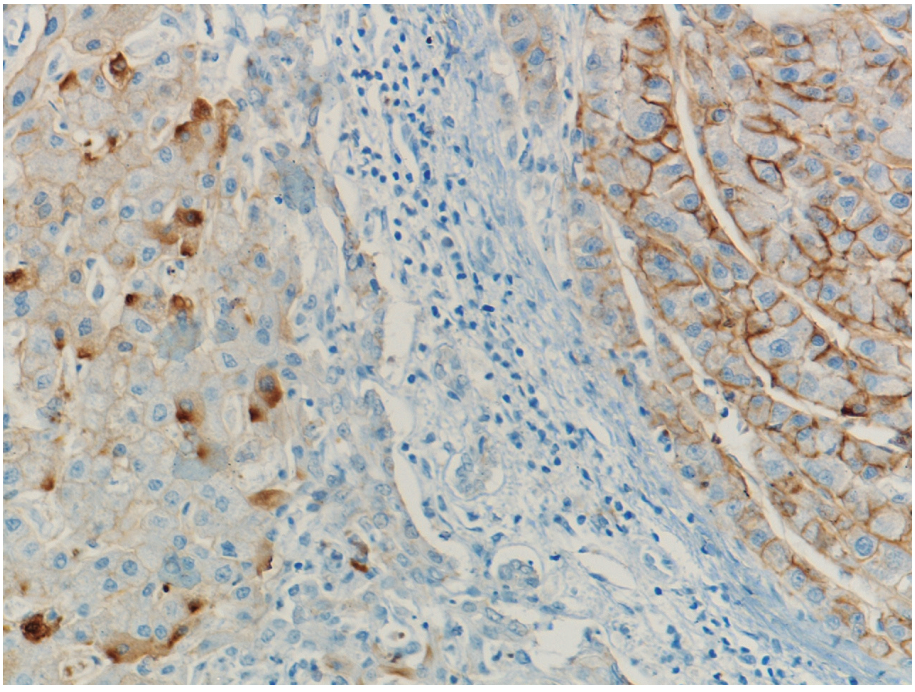

Fig. 2. Hepatocellular carcinoma grade II. Right: Intense membranous CD138 immunoexpression of tumour cells. Left: Adjacent non-neoplastic hepatocytes display mild membranous or, less frequently, cytoplasmic CD138 immunoexpression. x 200

Additionally, CD138 acts as a co-receptor in WNT signal transduction pathway in a HS-dependent manner, and affects the capability of WNT to induce accumulation of mammary progenitor cells (Liu et al.., 2004).

HGF (Hepatocyte Growth Factor) binds to HS chains of CD138 in myeloma cells, through c-*Met* receptor (Hepatocyte Growth Factor Receptor). This binding may result in: 1) HGF dimerization or oligomerization, thereby promoting Met cross-linking and tyrosine kinase activity, 2) conformational change of HGF, leading to enhanced signal transduction, 3) co-localization of CD138 and Met. Finally, HGF activates molecular transduction pathways of PI3∫ (Phosphatidyloinositol kinase-3) as well as Ras/MAPkinase (Mitogen Activated Protein Kinase) (Derksen et al., 2002). It is worth noting that in myeloma cells, heparanase overexpression increased HGF expression and ED-CD138 shedding, resuling in activation of the c-Met signaling pathway (Ramani et al., 2011).

CD138 overexpression boosts cell proliferation of endometrial cancer cells, through the NFkß (nuclear factor kß) signaling pathway (Oh et al., 2009). Additionally, experiments in breast cancer cell lines have shown that stromal CD138 expressed by fibroblasts stimulates cancer cell growth through an ED-CD138 shedding-dependent mechanism (Su et al., 2007).

2.1b Apoptosis

CD138 is implicated in molecular mechanisms that govern cell apoptosis. In myeloma cells, *sdc1* gene knockdown may cause growth arrest and apoptosis (Khostkaya et al., 2009) through a TRAIL (APO2-L) (TNF-Related Apoptosis-Inducing Ligand) extrinsic pathway (Wu et al., 2012). Furthermore, CD138 is involved in the PDK1/AKT/BAD (phosphoinositide-dependent kinase 1/v-akt murine thymoma viral oncogene homologue/Bcl2 antagonist of cell death) signaling pathway (Sun et al., 2011).

Evidence supports that membrane-bound CD138 and sCD138 have different roles: the former increasing cell proliferation, and the latter promoting apoptosis. These contradictory results may be explained by the fact that proteoglycans assemble as scaffolds which bring together different factors, in order to maintain homeostasis of cell proliferation and apoptosis (Teng et al., 2012).

2.2 CD138 and tumour invasion and metastasis

CD138 interacts with various ligands that are implicated in all steps of the multistage invasion-metastasis process. Alterations in CD138 immunoexpression have been correlated with tumour invasion and patients' poor overall survival in many types of cancer. In squamous cell head and neck carcinoma (Ishikawa and Kramer, 2010) and invasive ductal breast carcinoma (Vuoriluoto et al., 2008), CD138 may act as negative regulator of metastasis.

CD138 co-localizes with integrin α2ß1 and regulates actin binding on collagen type I. Moreover, crosstalk between CD138 and α2ß1 integrin may enhance MMP-1 transcription in response to collagen binding (Vuoriluoto et al., 2008). Experiments in mouse fibroblasts showed that CD138 makes an assembly and regulates integrin αvß5 (McQuade et al., 2006), while in breast cancer cell lines and endothelial cells CD138 controls αvß5 activation by connecting to IGF1R (Insulin-like Growth Factor 1 Receptor) (Beuvais et al., 2009). In addition, CD138 regulates integrin α6ß4, a member of an integrin subfamily that binds to laminin (Margadant et al., 2011).

The membrane-bound form of CD138 inhibits invasion in breast cancer cell lines (Nikolova et al., 2009) and fibrosarcoma (Endo et al., 2003), while the soluble-CD138 (equal to shed ED) (sCD138) has the opposite role. It is well worth noting that CD138 interacts with αvß3 and αvß5 through its ED (Beauvais et al., 2009). Furthermore, evidence supports the existence of a feedback loop between CD138 and MTI-MMP, as the membrane-bound form of CD138 inhibits MT-1MM,, whereas its ED that is cleaved by MT-1MMP induces invasion and metastasis. The exact molecular mechanism has not as yet been clarified (Vuoriluoto et al., 2011).

The distinct role of tumour and stromal CD138 immunoexpression in the regulation of cell anchorage, and thus in invasion and metastasis is also of great importance. When stromal fibroblasts overexpress CD138, the extracellular matrix organization is altered favouring increased mobility of breast cancer cells (Yang et al., 2011).

2.3. CD138 and angiogenesis

Angiogenesis is crucial in a tumour in order to maintain nutrient inflow and oxygen, and evacuate metabolic waste and carbon dioxide (Hanahan and Weineberg, 2011). Soluble-CD138 and the trans-membrane form of CD138 are implicated in tumour angiogenesis by locally increasing growth factors' concentration, mediating ligands' attachment to their receptors, and by directly interacting with angiogenic factor receptors. CD138 can bind to VEGF (Vascular Endothelial Growth Factor) and FGF-2 (fibroblast growth factor-2) and present them to the corresponding endothelial cell receptors to initiate the vascular budding process (Purusothaman et al., 2010).

CD138 is overexpressed by endothelial cells deriving from bone marrow of multiple myeloma patients. Furthermore, CD138 binds to and regulates VEGFR-2 (Vascular endothelial Growth Factor Receptor). Evidence supports that CD138 contributes to the maintenance of the receptor on the cellular membrane of endothelial cells, thus preventing CD138 recycling (Lamorte et al., 2012).

Soluble CD138, through its connection with

angiogenic factors, boosts angiogenesis in pro-metastatic tumour niches and its presence is essential for the proangiogenic action of integrins αvß3 and αvß5 (Purusothaman et al., 2010).

3. CD138 immunoexpression and human cancer

CD138 under normal conditions is predominantly expressed in epithelial cells and plasmacytes. As a biomarker, it is used to quantify plasmacytes in normal and neoplastic tissues, and also serves as a marker for the evaluation and classification of haematologic neoplasms (O'Connell et al., 2004). CD138 expression levels are particularly high in multiple myeloma cells (Sanderson and Yang, 2008).

In epithelial malignant neoplasms, CD138 is expressed by tumour cells and/or stromal cells. CD138 tumour immunohistochemical expression may be increased or decreased as compared to adjacent non-neoplastic tissue depending on the type of carcinoma and has been correlated with various clinico-pathological parameters and patients' prognosis. Table 1 summarizes data on CD138 tumour cell immunoexpression according to carcinoma type and its relationship with clinico-pathological variables and patient survival.

3.1 Carcinomas with increased CD138 immunoexpression

In urothelial carcinoma, CD138 immunoexpression is increased in neoplastic cells and correlates with high tumour grade, advanced disease stage, and tumour recurrence (Shimada et al., 2010).

In gallbladder carcinoma, increased CD138 protein levels in tumour cells have been correlated with lymph node metastasis and poor patient survival (Roh et al., 2008).

3.2 Carcinomas with reduced CD138 immunoexpression

3.2.1. Lung carcinoma

CD138 immunoexpression is reduced in primary lung carcinoma compared to adjacent non neoplastic tissue (Antonnen et al., 2001; Toyoshima et al., 2001; Shah et al., 2004; Al-Shibli et al., 2010). Low CD138

Table 1. Tumour cell CD138 immunoexpression in human carcinomas in relation to clinico-pathological parameters and patient prognosis.

	Tumour CD138 immunoexpression			
Carcinoma	CD138	Correlation with	Prognosis	Reference
Head & neck	↓	Tumour size; High grade; Advanced disease stage; Absence of lymph node metastasis	↓ survival	Inki et al., 1994; Pulkkinen et al., 1997; Anttonen et al., 1999; Chen and Ou, 2006; Kurokawa et al., 2006; Mathé et al., 2006; Ro et al., 2006; Martinez et al., 2009
Lung	↓	Poor differentiation	↓ survival	Antonnen et al., 2001; Toyoshima et al., 2001; Shah et al., 2004; Al-Shibli et al., 2010
Breast	↑↓	High grade; ER(-), PR(-); HER2 (+); High Ki 67 LI; Poor response to chemotherapy	↓ survival; ↓ disease-free; Survival	Barbareschi et al., 2003; Leivonen et al., 2004; Baba et al., 2006; Lofgren et al., 2007; Gotte et al., 2008; Loussouarn et al., 2008; Lendorf et al., 2011
Esophageal	↓	High grade; Advanced disease stage		Mikami et al., 2001; Szumilo et al., 2009
Gastric	↓		↓ survival	Watari et al., 2004; Wiksten et al., 2008; Huang et al., 2010
Colorectal	↓	Advanced disease stage; Poor differentiation; Lymph node metastasis	↓ survival	Day et al., 1999; Fujiya et al., 2001; Lundin et al., 2005; Hashimoto et al., 2008
Pancreatic	↑↓	Lymph node metastasis	↓ survival	Conejo et al., 2000; Juuti et al., 2005
Renal	↓	High grade		Godken et al., 2006
Gallbladder	↑	Presence of lymph node metastasis	↓ survival	Roh et al., 2008
Ovarian	↑↓	Advanced disease stage; Presence of lymph node metastasis	↓ survival	Davies et al., 2004; Kusumoto et al., 2010
Endometrial	↑↓	FIGO stage; Deep myometrial invasion; Presence of lymph node metastasis	↓ survival; ↓ disease-free; Survival	Hasengaowa et al., 2005; Choi et al., 2007; Kim et al., 2010
Cervical	↓	High grade		Rintala et al., 1999; Numa et al., 2002; Shinyo et al., 2005; Kim et al., 2011
Prostate	↑↓	Tumour dedifferentiation; High Gleason score; Serum PSA recurrence; Disease recurrence; Ki67 LI	↓ survival	Zellweger et al., 2003; Chen et al., 2004; Kiviniemi et al., 2004; Mennerich et al., 2004; Shariat et al., 2008; Contreras et al., 2010
Urinary bladder	↑	High grade; Advanced disease stage; Disease recurrence		Shimada et al., 2010

↑ increased, ↓ decreased CD138 immunoexpression, ↑↓ contradictory results, LI: labeling index.

immunoexpression is more common in high grade tumours (Anttonen et al., 2001) and is associated with poor prognosis both in small cell (Shah et al., 2004) and non small cell lung carcinoma (Anttonen et al., 2001).

3.2.2. Gastrointestinal carcinoma

Reduced CD138 immunoexpression in squamous oesophageal carcinoma is more frequently observed in high grade and advanced stage tumours (Mikami et al., 2001; Szumilo et al., 2009) and is a marker of poor patient survival (Watari et al., 2004; Wiksten et al., 2008; Huang et al., 2010). In colorectal carcinoma, as well as in high grade dysplasia, CD138 immunoexpression is reduced compared to adjacent normal colonic epithelium (Day et al., 1999; Fujiya et al., 2001; Lundin et al., 2005; Hashimoto et al., 2008). Reduced CD138 tumour cell expression is associated with high histological grade, advanced disease stage (Lundin et al., 2005; Hashimoto et al., 2008), lymph node metastasis (Fujiya et al., 2001; Hashimoto et al., 2008), and is an independent marker of poor patient survival (Fujiya et al., 2001).

3.2.3. Renal carcinoma

Reduction of CD138 immunoexpression in renal cell carcinoma has been correlated with increased nuclear grade and is independent of tumour histological subtype (Godken et al., 2006).

3.2.4. Cervical carcinoma

Decreased CD138 protein expression and simultaneous translocation of CD138 from the cell membrane to the cytoplasm are considered to be early events in the progression of cervical intraepithelial neoplasia to early invasive cancer (Shinyo et al., 2005) and characterize invasive carcinoma (Rintala et al., 1999; Numa et al., 2002; Shinyo et al., 2005; Kim et al., 2011). Low CD138 immunoexpression in cervical adenocarcinoma positively correlates with high tumour grade (Inki et al., 1994).

3.2.5. Head and Neck Carcinoma

Reduction of tumour cell CD138 immunoexpression has been observed in head and neck squamous cell carcinoma (Inki et al., 1994; Pulkinnen et al., 1997, Anttonen et al., 1999; Chen et al., 2006; Mathé et al., 2006; Ro et al., 2006) and has been correlated with increased tumour size (Inki et al., 1994, Anttonen et al., 1999; Ro et al., 2006), high grade (Anttonen et al., 1999; Ro et al., 2006; Kurokawa et al., 2006), advanced disease stage (Anttonen et al., 1999; Chen et al., 2006) and presence of lymph node metastasis (Bayer-Garner et al., 2000). Similar findings are reported in carcinoma of the tongue. Survival analyses highlight low CD138 protein expression as a marker of poor prognosis in patients with head and neck carcinoma (Chen et al., 2006; Mathe et al., 2006; Ro et al., 2006; Stepp et al., 2010), including nasopharyngeal carcinoma (Chen et al., 2006).

3.2.6 Skin Carcinoma

CD138 immunoexpression is reduced in squamous and basal cell carcinoma (Bayer-Garner et al., 2000; Stepp et al., 2010). It has been suggested that CD138 may serve as a biomarker to distinguish extramammary Paget's disease (cytoplasmic CD138 immunostain), pagetoid Bowen's disease (membranous CD138 immunostain) and pagetoid *in situ* malignant melanoma (complete loss of CD138 immunoexpression) (Bayer-Garner and Reed, 2004).

3.3. Carcinomas with contradictory results on CD138 immunoexpression

3.3.1. Thyroid carcinoma

The majority of data show that CD138 immunoexpression is increased in thyroid carcinoma cells, while in only one study it was decreased in comparison to non-neoplastic thyroid follicle cells (Mitselou et al., 2007). Anaplastic thyroid carcinomas have higher levels of CD138 compared to follicular and papillary carcinoma. In both papillary and follicular carcinoma, CD138 protein expression may be related to invasion and is higher in cases with extracapsular tumor extension (Ito et al., 2003; Bologna-Molina et al., 2010).

3.3.2. Breast carcinoma

In breast carcinoma, most studies show that CD138 immunoexpression is increased (Barbareschi et al., 2003; Leivonen et al., 2004; Baba et al., 2006; Gotte et al., 2006; Lendorf et al., 2011) and correlates with negative estrogen and progesterone receptor immunoexpression, ERB,2 (HER2/neu) immunopositivity (Barbareschi et al., 2003), high Ki67 index (Barbareschi et al., 2003; Baba et al., 2006; Lendorf et al., 2011), poor response to chemotherapy (Götte et al., 2006), and poor disease-free and overall survival (Barbareschi et al., 2003; Baba et al., 2006). Overexpression of CD138 has been observed in cases with axillary lymph node metastasis (Thanakit et al., 2008). In contrast to the above, other studies (Lofgren et al., 2007; Loussouarn et al., 2008) have shown that reduced CD138 expression in breast carcinoma cells is correlated with high tumour grade and poor disease-free survival (Loussouarn et al., 2008).

3.2.3. Ovarian carcinoma

According to Davies et al. (2004) and Salani et al. (2007) CD138 tumour cell expression is increased in ovarian carcinoma. In contrast, reduced CD138 immunoexpression has been correlated with advanced

disease stage, presence of lymph node metastasis and poor patient overall survival (Kusomoto et al., 2010).

3.3.4. Endometrial adenocarcinoma

Overexpression of CD138 in endometrial hyperplasia may correlate with advanced risk of developing endometrial adenocarcinoma (Choi et al., 2007; Kim et al., 2010). In contrast, Hasengaowa et al. (2005) have shown that CD138 immunoexpression is decreased in endometrial adenocarcinoma and correlates with advanced FIGO stage, deep myometrial invasion, lymph node metastases and poor disease-free and overall survival.

3.3.5. Prostate adenocarcinoma

Reduction of CD138 immunoexpression is a common finding in prostate adenocarcinoma (Chen et al., 2004; Kiviniemi et al., 2004; Shariat et al., 2008; Contreras et al., 2010; Suhovskih et al., 2013) and in one study was accompanied by change in the topography of CD138 immunostaining from the cell membrane to the cytoplasm (Contreras et al., 2010). Decreased CD138 in tumour cells is more common in locally invasive prostate adenocarcinomas and has been correlated with tumour dedifferentiation (Kiviniemi et al., 2004), high Gleason score (Contreras et al., 2010), high serum PSA levels and disease recurrence (Chen et al., 2004).

In contrast, Zellweger et al. (2003) reported that increased CD138 in tumour cells correlates with high Gleason score, increased cell proliferation, tumour recurrence and poor survival. The prognostic significance of CD138 immunoexpression in prostate cancer has been questioned by some authors (Brimo et al., 2010).

3.3.6. Pancreatic adenocarcinoma

Conejo et al. (2000) have shown that CD138 is overexpressed in pancreatic ductal carcinoma and correlates with lymph node metastasis, while others report that it is decreased (Juuti et al., 2005; Kylänpää et al., 2009) and is a marker of poor survival (Juuti et al., 2005).

3.3.7. Liver carcinoma

In hepatocellular carcinoma (HCC), decreased CD138 immunoexpression has been correlated with high grade (Li et al., 2005), tumour recurrence and presence of intrahepatic and extrahepatic metastasis (Matsumoto et al., 1997; Li et al., 2005; Lu et al., 2006). Fibrolamellar HCC also show decreased CD138 compared to conventional HCC (Patonai et al., 2012). In contrast, other studies show a trend for CD138 overexpression in poorly differentiated HCC (Ramalingam et al., 2008). Tiniakos et al. (2009) have reported that a reduction of CD138 membranous immunoexpression in HCC is correlated with tumour dedifferentiation (Fig. 2). Moreover, CD138 immunoexpression emerged as an independent marker of poor prognosis in a cohort of Greek HCC patients (Tiniakos, et al., 2011). In cholangiocellular carcinoma, a reduction of CD138 immunoexpression has been correlated with lymph node metastasis and poor patient survival (Harada

Table 2. Stromal cell CD138 immunoexpression in human carcinomas in relation to clinico-pathological parameters and patient prognosis.

Stromal CD138 immunoexpression				
Carcinoma	CD138	Correlation with	Prognosis	Reference
Head & neck	+	Recurrence	↓ survival	Mathé et al., 2006
Thyroid	+	Tumour size		Ito et al., 2003; Bologna-Molina et al., 2010
Breast	+/-	Vascular density		Götte et al., 2006; Maeda et al., 2006; Lofgren et al., 2007; Loussouarn et al., 2008
Esophageal	+	Tumour dediffentiation; Distant metastasis		Szumilo et al., 2009
Gastric	+		↓ survival	Wiksten et al., 2001, 2008
Colorectal	+/-	No correlation		Day et al., 1999; Lundin et al., 2005; Hashimoto et al., 2008
Pancreatic	+/-		↓ survival	Conejo et al., 2000; Juuti et al., 2005
Ovarian	+	Disease stage; Ascites; Lymph node metastasis	↓ survival	Davies et al., 2004; Kusumoto et al., 2010
Endometrial	+/-		↓ survival	Hasengaowa et al., 2005; Choi et al., 2007
Prostate	-			Chen et al., 2004; Mennerich et al., 2004; Shariat et al., 2007
Urinary bladder	+			Mennerich et al., 2004

+: positive, - : negative CD138 stromal immunoexpression.

et al. 2003).

3.4. Stromal CD138 immunoexpression in human carcinoma

Tumour development and metastasis are accompanied by simultaneous alteration of the microenvironment through paracrine communication (Hanahan and Weinberg et al., 2011). Endothelial cells, fibroblasts, pericytes and leukocytes in tumour microenvironment play pivotal roles in various signal transduction pathways (Pietras and Ostman, 2010).

Stromal CD138 expression has been correlated with clinical data and histopathological parameters in many human carcinomas. Table 2 summarizes these data according to carcinoma type and relationship to clinico-pathological variables and patient survival.

3.4.1 Immunohistochemical studies on stromal CD138 immunoexpression

In head and neck carcinoma, stromal CD138 immunoexpression has emerged as an independent marker of tumour recurrence and poor patient survival (Mathé et al., 2006).

In breast carcinoma, data are conflicting (Lofgren et al., 2007; Gotte et al., 2006; Thanakit et al., 2008). Stromal CD138 immunopositivity has been associated with high microvascular density (Maeda et al., 2006) and was decreased after chemotherapy (Tokes et al., 2009).

In oesophageal carcinoma, stromal CD138 immunoexpression has been correlated to tumour dedifferentiation and presence of distant metastasis (Szumilo et al., 2009), while in gastric carcinoma it may mark poor patient survival (Watari et al., 2004; Wiksten et al., 2001). In colorectal carcinoma, results are contradictory and do not correlate with clinico-pathological parameters (Lundin et al., 2005; Hashimoto et al., 2008).

In pancreatic adenocarcinoma, stromal CD138 immunoexpression was not observed by Conejo et al. (2000). In contrast, Juuti et al. (2005) highlighted its presence and showed that it is an independent marker of poor prognosis.

In ovarian carcinoma, stromal CD138 immuno-expression is associated with serous histological subtype, advanced tumour stage, ascites, lymph node metastasis (Kusumoto et al., 2010) and is an independent marker of poor patient survival (Davies et al., 2004; Kusumoto et al., 2010).

In endometrial adenocarcinoma, Kim et al. (2010) observed stromal CD138 immunoexpression that was associated with tumour progression and poor prognosis, while Choi et al. (2007) commented on rare CD138 stromal immunopositivity without any correlation to clinico-pathological parameters (Choi et al., 2007).

In prostate carcinoma, no stromal CD138 immunoexpression has been observed by Chen et al. (2004), Mennerich et al., (2004) Shariat et al. (2008). In contrast, Suhovskih et al. (2013) highlighted its presence. CD138 overexpression by stromal cells has been observed in urinary bladder carcinoma (Mennerich et al., 2004).

In thyroid carcinoma, stromal CD138 immuno-expression has been correlated with tumour size (Contreras et al., 2010) and it was more intense in anaplastic compared to follicular or papillary carcinoma (Ito et al., 2003). In papillary carcinomas, CD138 stromal expression was more frequent in those with extracapsular invasion (Contreras et al., 2010).

3.4.2 Origin of stromal CD138 immunoexpression

What is the origin of the stromal CD138 immuno-expression? Is CD138 produced by stromal cells or is the shed ectodomain of CD138 (sCD138) uptaken by stromal cells? Experiments in breast cancer cell lines have shown that the answers to these questions are complicated. Breast cancer cells induce the production of CD138 by stromal fibroblasts and at the same time stromal fibroblasts induce breast cancer cell growth through a mechanism depending on sCD138 shedding (Mennerich et al., 2004). In a xenograft model, breast cancer cells inoculated into athymic nude mice induce accelerated tumour growth only when mixed with CD138-transfected fibroblasts (Maeda et al., 2006).

In the majority of studies the anti-CD138 antibodies used bind only to the ED (sCD138) of CD138 [clones BB4 (Su et al., 2007) or MI15 (Gattei et al., 1995)]. Consequently, it is unclear if the observed stromal CD138 immunoexpression corresponds to sCD138, to the whole CD138 molecule produced by stromal cells, or to both. Only in oral carcinoma, the use of antibodies specific for extracellular or cytoplasmic domain epitopes have clarified that stromal CD138 expression indeed originates in stromal cells (Mathé et al., 2006).

3.5 Nuclear CD138 immunoexpression and cancer

In addition to the membranous and cytoplasmic immunolocalisation of CD138, evidence supports its presence, as well as the presence of heparanase, in the nucleus of tumour cells (Brockstedt et al., 2002). Nuclear CD138 inhibits HAT (Histone Acetyl Transferase) suppressing the expression of many genes. Shedding of CD138 by heparanase leads to gene activation (Ramani et al., 2013).

Nuclear CD138 immunoexpression has been reported in a small fraction of HCC tumour cells (Roskams et al., 1998) and in mesothelioma (Saqi et al., 2005). In the latter, absence of membranous CD138 immunoexpression was proposed to aid differential diagnosis from carcinoma (Saqi et al., 2005).

4. Serum sCD138 as a biomarker in cancer

Increased values of serum sCD138 are of prognostic significance in some haemopoietic malignancies,

including multiple myeloma (Seidel et al., 2000; Lovell et al., 2005) and chronic lymphocytic leukemia (Molica et al., 2006; Jilani et al., 2009), but not in Hodgkin lymphoma (Vassilakopoulos et al., 2005).

In lung cancer, increased pre-treatment (chemotherapy and/or surgery) serum values of sCD138 are a marker of poor patient prognosis independently of disease stage (Joensuu et al., 2002; Anttonen et al., 2003, 2006). In laryngeal and hypo-pharyngeal carcinoma, reduction of serum sCD138 levels after radiotherapy is a marker of good prognosis, while its increase is an indicator of tumour recurrence (Anttonen et al., 2006). In HCC, elevated serum sCD138 has been correlated with advanced disease stage (Metwaly et al., 2012), greater risk of tumour recurrence and poor overall patient survival (Nault et al., 2013)

5. Perspectives

CD138 is an attractive molecular therapeutic target for many types of cancer. Indeed, applied research focuses on the development of heparanase inhibitors (Theocharis et al., 2010; Ramani et al., 2013). The heparanase inhibitor PI-88 has anti-angiogenic properties and is now in phase III clinical trial in hepatitis virus-related HCC. PG545 heparanase inhibitor shows anti-tumour and anti-metastastic activity in animal models of cancer (Ramani et al., 2013). SST001 has *in vivo* and *in vitro* anti-angiogenic function that inhibits CD138 ED shedding and decreases HGF, VEGF and MMP9 expression (Ritchie et al., 2011). In preclinical models, SST001 showed anti-neoplastic activity in Ewing sarcoma, myeloma and in pancreatic cancer (Ramani et al., 2013). Heparanase action may also be inhibited using specific microRNAs, like miRNA-258 which blocks heparanase expression and decreases metastasis in breast cancer cells (Ramani et al., 2013).

The targeted inhibition of CD138 expression using monoclonal antibodies is another promising therapeutic approach. The fully human antibody OC-46F2, specific for the ED domain of syndecan-1, can inhibit vascular maturation and tumour growth in experimental human melanoma. OC-46F2 showed therapeutic efficacy in experimental ovarian carcinoma (Orecchia et al., 2013). Another anti-CD138 monoclonal antibody, nBT062, when conjugated with high toxicity molecules, slowed the progression of multiple myeloma and increased survival of animals in xenograft and SCID-hu mouse models (Ikeda et al., 2009).

Inhibition of CD138 at the mRNA level has also been used as an anticancer strategy. Zoledronate, a biphosphonate with antitumour properties, inhibits CD138 mRNA expression disrupting CD138-integrin αvß3 crosstalk in breast cancer cells (Dedes et al., 2012). Synstatin, a synthetic peptide that antagonizes CD138 core protein, inhibits IGF1R-avb3 integrin complex formation leading to inhibition of angiogenesis and tumour growth (Rapraeger, 2013).

Data from the reviewed literature have highlighted CD138 (serum sCD138 and/or immunohistochemical) expression as a potential prognostic biomarker in many types of carcinomas. Further studies are needed to confirm the existing evidence on the prognostic significance of CD138 immunophenotype.

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