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The Adhesion Molecule L1CAM as a Novel Therapeutic Target for Treatment of Pancreatic Cancer Patients?

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly malignant tumor disease with a still dismal prognosis for the patients. Since the tumor is mostly detected only in an advanced stage when the tumor has already metastasized, therapeutic options are quite limited. Moreover, this tumor is characterized by a profound resistance towards cytostatic drugs essentially hampering chemotherapy and reducing survival times of PDAC patients. The expression of the adhesion molecule L1CAM (CD171) has been recently reported to be associated with a chemoresistant and migratory phenotype of PDAC cells. L1CAM is a member of the immunoglobulin superfamily and has been initially found to play a role during the development of the nervous system. Meanwhile, L1CAM has been detected in numerous cancer tissues including PDAC and its elevated expression correlates with poor prognosis for the patients. Moreover, L1CAM has been shown to play an important role in different cellular processes involved in tumorigenesis such as cell migration and invasion, proliferation, survival and chemoresistance. Accordingly, inhibition of L1CAM by means of RNA interference or antibody-mediated blockade markedly reduced migration and proliferation of tumor cells and increased their chemosensitivity. Several preclinical studies e.g. in mouse model sytems for PDAC already demonstrated considerable anti-tumor effects with significantly reduced tumor outgrowth and tumor cell dissemination along with prolonged survival. Altogether, these data point to the suitability of L1CAM as a therapeutic target for an improved therapy of PDAC.

This chapter will describe the current knowledge on the physiological and pathophysiological role of the adhesion molecule L1CAM with an emphasis on its broad pro-tumorigenic functions and, in particular, its role in PDAC. Furthermore, we will figure out the underlying mechanisms and will summarize the preclinical studies on the specific targeting of L1CAM in anti-cancer therapy.

2. L1CAM – structure and physiological function

The adhesion molecule L1CAM (CD171) is a 220 kD transmembrane glyocoprotein and belongs to the immunoglobulin superfamily. The extracellular part of the molecule

comprises six Ig-like domains followed by 5 fibronectin type III repeats. The transmembrane domain is followed by a short cytoplasmic tail of 32kD (Hortsch, 1996; Weidle et al., 2009) (Figure 1). L1CAM can be expressed and mediate its effects as a membrane-bound form but it can also be proteolytically cleaved by different proteases releasing a soluble ectodomain that is likewise functionally active. To date, the metalloproteases ADAM 10 and 17 as well as plasmin have been described to cleave L1CAM generating a soluble 200 kD and 150 kD form, respectively (Maretzky et al., 2005; Mechtersheimer et al., 2001; Weidle et al., 2009) (Figure 1). After ADAM-mediated cleavage, the membrane-bound intracellular C-terminal fragment of L1CAM can be further processed by the presenilin/γ-secretase complex giving rise of a 28 kD fragment (Maretzky et al., 2005). This small intracellular fragment translocates into the nucleus where it is thought to contribute to L1CAM-dependent gene regulation (Maretzky et al., 2005; Riedle et al., 2009).

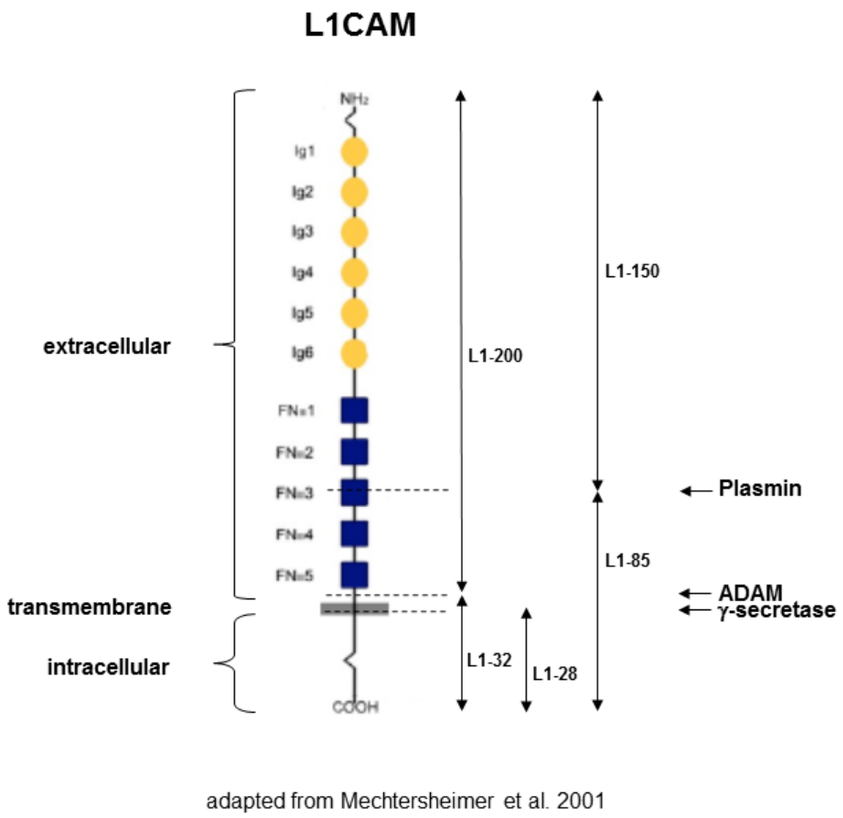

Fig. 1. **Scheme of the L1CAM molecular structure.** The extracellular, transmembrane and intracellular domains are indicated on the left. Cleavage sites for different proteases (plasmin, ADAM, γ-secretase) are indicated by the arrow heads and the dashed lines. The respective cleavage products (L1-200, L1-150, L1-85, L1-32, L1-28) are indicated by the vertical arrowed lines**.**

L1CAM can bind to different substrates/molecules in a cell and context dependent manner. Thus, it can undergo homophilic binding to itself as a membrane-bound or shedded form (de Angelis et al., 1999). In addition, a plethora of other proteins have been described with which L1CAM can interact, e.g. integrins αvβ3, α5β1, αvβ1 or αvβ5 (Ebeling et al., 1996;

Montgomery et al., 1996; Oleszewski et al., 1999) as well as neuropilin-1 (Stoeck et al., 2005), CD24 (Kadmon et al., 1995), neurocan (Oleszewski et al., 1999) and axonin-1/TAX-1 (Kuhn et al., 1991).

L1CAM was originally identified in cells of the nervous system (Rathjen & Schacher, 1984) and is regarded as a major player in its development being involved in neurite outgrowth and fasciculation, synapse formation as well as neuronal cell survival in the developing and adult brain (Hortsch, 1996; Loers et al., 2005; Maness & Schachner, 2007). The pivotal role of this adhesion molecule in the nervous system is underscored by the fact that mutations of the L1CAM gene cause severe neurodevelopmental disorders referred to as L1 syndrome or CRASH syndrome (Fransen et al., 1997; Weller et al., 2001). The different mutations and their resulting malfunctions of L1CAM in the nervous system are outlined in more detail in a recently published review (Schäfer & Altevogt, 2010). The L1CAM gene is located at chromosome Xq28 comprising 28 exons. Two splicing variants of L1CAM have been identified, the full-length form which is predominantly expressed by neuronal cells and a shorter non-neuronal isoform lacking exon 2 and exon 27 which is expressed by most types of cancer (de Angelis et al., 2001; Gast et al., 2005; Geismann et al., 2011; Kallunki et al., 1997; Meli et al., 1999; Shtutman et al., 2006). Besides its expression on neuronal cells, L1CAM expression has been also found in certain populations of hematopoietic cells (Ebeling et al., 1996; Pancook et al., 1997) and recent reports suggested a role for L1CAM in transendothelial migration and trafficking of murine dendritic cells (Maddaluno et al., 2009). Furthermore, L1CAM is expressed by renal tubular epithelial cells under physiological conditions being involved in branching of renal tubes in the kidney (Debiec et al., 1998). However, distribution of L1CAM in adults is quite restricted so that its elevated expression in cancerous tissues which is discussed in the next paragraph favours its suitability as therapeutic target in anti-cancer therapy.

3. L1CAM expression in tumors

To date, two comprehensive analyses on L1CAM tissue expression have been performed using a wide array of different normal and tumor tissues (Huszar et al., 2006; Rawnaq et al.; 2010). Moreover, systematic analyses of L1CAM expression in many types of tissues and tumors provided additional data on L1CAM expression in cancer and cancer related diseases. Elevated expression of L1CAM has meanwhile been detected in a variety of tumors such as neuroblastoma, glioma, melanoma, gynaecological tumors, colon cancer and gastrointestinal stromal tumors (GIST) (reviewed in Raveh et al., 2009). Tumoral L1CAM expression is often found at the invasive front of primary tumors (Gast et al., 2005; Zecchini et al., 2008) strongly supporting a role for L1CAM in metastasis. Hence, elevated tumor associated L1CAM expression correlates with tumor cell dissemination in lymph nodes and the bone marrow indicating micrometastatic spread (Kaifi et al., 200), more advanced tumor stages (Li & Galileo, 2010) and consequently reduced patient´s survival (Fogel et al., 2003; Kaifi et al., 2007; Zecchini et al., 2008). Besides L1CAM expression in tumor tissues, soluble L1CAM was detectable in the serum of 80 % and 90% of ovarian and uterine carcinoma patients at stage III-IV, respectively (Fogel et al., 2003). Zander et al. recently demonstrated that serum concentrations of soluble L1CAM were also elevated in GIST patients compared to healthy controls being particularly enhanced in patients with recurrence and relapse (Zander et al., 2011).

3.1 L1CAM expression in pancreatic tumors

Regarding the expression of L1CAM in PDAC, discrepant data have been published. This might rely on the variable usage of i) the number of analysed tissues, ii) tissue microarrays versus areal sections, iii) detection methods (mostly immunohistochemistry but also western blotting, microarrays), iv) staining protocols (e.g. the pH during antigen retrieval essentially impacts on the staining intensity) and v) scoring systems to determine L1CAM positivity. With respect to the latter, determination of L1CAM positivity can occur e.g. by scoring the staining intensity (weak = < 30% of tumor cells L1CAM+, strong= > 30% of tumor cells L1CAM+) (Rawnaq et al., 2010) or by consideration of tissue samples L1CAM positive when more than 10% of tumor cells exhibited a strong membranous staining (Huszar et al., 2006).

An analysis of a small number of samples by Huszar et al. revealed no L1CAM expression in PDAC and pancreatic neuroendocrine tumors (Huszar et al., 2006). Kaifi et al. demonstrated L1CAM expression in 2 % (2/111 samples) of PDAC and 7,9 % of pancreatic neuroendocrine tumors (5/63 cases). In the latter, L1CAM expression was mostly found in poorly differentiated pancreatic neuroendocrine carcinomas that are described to have the worst prognosis (Kaifi et al., 2006a, 2006b; Rawnaq et al., 2010). A study with 15 tissues of undifferentiated (anaplastic) pancreatic cancer and pancreatic carcinoma with osteoclast-like giant cells revealed L1CAM positivity in 80 % of the analysed samples (Bergmann et al., 2010a). Our group was the first who documented considerable L1CAM expression in a small series of PDAC samples (Sebens Müerköster et al., 2007). An extended analysis with 110 primary PDAC tissues, 15 lymph node and 14 liver metastases revealed tumoral L1CAM expression in 92,7 %, 80 % and 100 % of the samples, respectively (Bergmann et al., 2010b). Another study demonstrated L1CAM expression in 82 % of poorly-differentiated and in 14 % of moderately-differentiated PDAC tumors being absent in well-differentiated PDAC and normal pancreatic tissues (Chen et al., 2011). In line with these data, Ben et al. described L1CAM positivity in PDAC correlating with nodal involvement, vascular and perineural invasion, a higher degree of pain and accordingly with poor survival (Ben et al., 2010). Similarly, Tsutsumi et al. reported L1CAM expression in 23/107 PDAC samples (21,5 %) being predominantly found at the invasive front of the tumors. Again, L1CAM expression was significantly associated with histological grade, lymph node involvement, metastasis and short survival (Tsutsumi et al., 2011). Recently, a functional genome approach analysing PDAC tissues compared to normal pancreatic tissues identified a panel of seven differentially expressed genes including L1CAM which was named “migration signature” according to the functional involvement of the deregulated genes in tumorigenesis (Balasenthil et al., 2011). In search for the mechanisms leading to upregulation of L1CAM in tumors, we analysed pancreatic precursor lesions such as Pancreatic Intraepithelial Neoplasias (PanINs) and tissues of chronic pancreatitis. Indeed, considerable L1CAM expression - albeit weaker than in tumors - was already found in PanINs predominantly in high-grade PanINs 2 and 3 (Bergmann et al., 2010b) as well as in the majority of chronic pancreatitis (Geismann et al., 2009).

In summary, L1CAM expression is found – albeit at varying degree – in PDAC and correlates with advanced tumor stage, poor prognosis and short survival. Notably, L1CAM expression is already present in precursor lesions of PDAC and later on in tumor cells in primary tumors and metastases pointing to a role of this adhesion molecule in pancreatic tumorigenesis. This will be outlined in more detail in the next paragraph.

4. L1CAM function in tumorigenesis

L1CAM expression in tumors can be associated with the activation of several signalling pathways that are known to play a pivotal role in tumor progression e.g. the MAPK/ERK and AKT pathway or FAK-mediated signalling. Current knowledge on the L1CAM-mediated cellular alterations in tumorigenesis largely derived from studies with various types of tumor cells. Nevertheless, these alterations seem to be relevant also in pancreatic tumorigenesis and we will therefore discuss findings on the role of L1CAM in tumor manifestation and progression from studies with PDAC as well as other tumor entities. We also like to refer to the excellent reviews outlining in more detail the current knowledge on L1CAM-mediated signalling (Herron et al., 2009; Kiefel et al., 2011).

4.1 L1CAM and EMT

Epithelial-mesenchymal transition (EMT) represents a key event in the transformation process of an epithelial cell and is characterized by morphological and phenotypical alterations. Through EMT, epithelial/carcinoma cells acquire a motile phenotype so that they become enabled to leave the cellular context and disseminate into distant organs. The first hint that L1CAM might be connected with EMT was provided by the group of Shtutman (Shtutman et al., 2006). In the mamma carcinoma cell line MCF7, L1CAM expression leads to the disruption of E-cadherin- containing adherens junctions and thereby to increased transcriptional activity of β-catenin (Shtutman et al., 2006). Since L1CAM is a target gene of β-catenin signalling (Gavert et al., 2005), activation of β-catenin contributes to sustained L1CAM expression and enhanced cell motility in the cells (Shtutman et al., 2006). In line with these findings, immunohistochemical stainings of endometrial carcinomas revealed L1CAM expression at the leading edge of the tumor while E-cadherin expression was lost which could be linked to an aggressive subtype of this tumor (Huszar et al., 2010). Stimulation of endometrium carcinoma cells with the well-known EMT inducer TGF-β1 led to the upregulation of vimentin and concomitantly to the downregulation of E-cadherin depending on the transcription factor Slug. As a result, stimulated LCAM expressing tumor cells acquired a migratory phenotype (Huszar et al., 2010). In contrast, Gavert et al. recently showed that L1CAM mediated metastasis of colon cancer cells was dispensable of EMT induction and an altered expression of epithelial and mesenchymal marker proteins (Gavert et al., 2011). Thus, the impact of L1CAM on EMT might be either tumor specific and/or tumor stage dependent. However, stimulation of pancreatic ductal epithelial cells with TGF-β1 led to the acquisition of a spindle-shaped cell morphology, upregulation of mesenchymal proteins and L1CAM expression which was dependent on JNK-mediated activation of Slug (Geismann et al., 2009). Accordingly, elevated cell migration and apoptosis resistance could be abolished by interfering with TGF-β1 signalling or by suppression of Slug or L1CAM. Further studies are required to elaborate whether upregulation of L1CAM is part of the EMT or even the inducing event.

4.2 L1CAM and cell motility and migration

On the one hand, the importance of L1CAM for cell migration, invasion and metastasis is based on the detection of L1CAM expressing tumor cells in metastases as well as at the invasive front of the primary tumor (Bergmann et al., 2010b; Chen et al., 2011; Gavert et al.,

2005; Kaifi et al., 2007). On the other hand, numerous in vitro and in vivo studies provide compelling evidence for the role of L1CAM in cell migration of various tumor entities such as ovarian cancer (Arlt et al., 2006; Gast et al., 2005; Zecchini et al., 2008), colon cancer (Gavert et al., 2005; Gavert et al., 2011), melanoma (Meier et al., 2006), glioma (Yang et al., 2009; Yang et al., 2011), glioblastoma stem cells (Cheng et al., 2011), breast cancer (Li & Galileo, 2010) and PDAC (Chen et al., 2010; Geismann et al., 2009). Cleavage of L1CAM seemed to be a prequisite for promoting the adhesion and migration of breast cancer cells (Li & Galileo, 2010) as well as for the motility of glioma (Yang et al., 2009), ovarian cancer (Mechtersheimer et al. 2001) and colon cancer cells (Gavert et al., 2005). In the latter, ADAM 10 has been shown to enhance L1CAM cleavage in L1CAM expressing colon cancer cells and to induce liver metastasis in a mouse model system (Gavert et al., 2007). In addition, ligation of L1CAM to integrins such as αvβ3 (Meier et al., 2006) or αvβ5 (Mechtersheimer et al., 2001) seemed to be pivotal for L1CAM-mediated cell migration leading to the activation of Erk1/2 (Gast et al., 2007) and FAK signalling (Yang et al., 2011). As a result of the L1CAM-mediated Erk1/2 activation genes encoding for pro-migratory proteins such as cathepsin-B or α3-integrins were upregulated (Gast et al., 2007). Besides its ability to induce Erk1/2 and FAK signalling pathways, L1CAM can also lead to the activation of NF-κB, so that inhibition of NF-κB reduced L1CAM-mediated metastasis of colon cancer cells (Gavert et al., 2010).

4.3 L1CAM and angiogenesis

Besides its ability to directly increase motility and migratory behavior of tumor cells, L1CAM might also promote metastasis via its pro-angiogenic properties. Thus, soluble L1CAM was able to stimulate growth and invasion of bovine aortic endothelial cells to a similar extent as the vascular endothelial growth factor VEGF-A_{165} (Friedli et al., 2009). Moreover, stimulation with soluble L1CAM led to tube formation of bovine aortic endothelial cells *in vitro* and increased angiogenesis *in vivo* (Friedli et al., 2009). The pro-angiogenic effect of soluble L1CAM could be abolished by treatment with the L1CAM specific antibody chCE7. Issa et al. showed that endothelial cells in PDAC are characterized by elevated L1CAM expression compared to HUVEC cells where L1CAM expression can be induced by TNF–α, IFN–γ or TGF-β1 (Issa et al., 2009). Antibody-mediated blockade of L1CAM abolished tube formation and tumor endothelial cell transmigration (Issa et al., 2009). Overall, these data point to a role of L1CAM as a pro-angiogenic factor and the potential of an anti-L1CAM antibody therapy in interfering with tumor angiogenesis (see below).

4.4 L1CAM and cell growth

Overexpression of L1CAM has been shown to promote tumor cell proliferation. Accordingly, inhibition of L1CAM expression or function suppresses proliferation of tumor cells, e.g. in cholangiocarcinoma (Min et al. 2010) or ovarian carcinoma (Arlt et al., 2006; Novak-Hofer et al, 2008). Zecchini et al. confirmed the stimulating effect of L1CAM on proliferation of ovarian cancer cells and additionally demonstrated that L1CAM expression does not alter proliferation of non-tumorigenic ovarian epithelial cells (Zecchini et al., 2008). Moreover, inhibition of L1CAM by genetic interference or antibody-mediated blockade impaired growth of tumor cells resulting in a reduced phosphorylation of Erk1/2 (Arlt et al.,

2006; Zecchini et al., 2008). Cotreatment of SKOV3ip ovarian carcinoma cells with anti-L1CAM antibodies and the soy-derived isoflavone Genistein potentiated the anti-proliferative effects of the anti-L1CAM antibody along with reduced activation of Erk1/2, Akt and Src kinase (Novak-Hofer et al., 2008). The growth promoting effect of L1CAM can be attributed to the activation of the Erk1/2 and Akt-pathway of which both are known to accelerate proliferation and growth of tumor cells (Gast et al., 2007, Novak-Hofer et al., 2008). For the induction of these signalling pathways, the interaction with integrins seems to be important as well as the cytoplasmic part of L1CAM because mutations in the RGD binding site which mediates binding to integrins or of the cytoplasmic tail abrogated L1CAM-mediated signalling and cellular responses (Gast et al., 2007; Sebens Müerköster et al., 2009; Kiefel et al., 2011).

4.5 L1CAM and apoptosis resistance

Besides its role in proliferation, several reports show that L1CAM is involved in apoptosis resistance. Loers et al. reported on a role for L1CAM in neuroprotection (Loers et al., 2005) by conferring protection from apoptosis induction in neuronal cells. In their experiments, murine cerebellar neurons grown on L1CAM substrate were protected from apoptosis induced by serum deprivation, oxidative stress and staurosporine treatment. L1CAM-mediated apoptosis resistance was associated with enhanced activation of Erk1/2, Akt and Bad as well as inhibition of caspases (Loers et al., 2005). Our group demonstrated that L1CAM plays a pivotal role in the mediation of chemoresistance of tumor cells which is a hallmark of PDAC. Thus, L1CAM expressing PDAC cell lines such as Colo357 and Panc1 responded much less towards treatment with cytostatic drugs than cells lacking L1CAM expression (Sebens Müerköster et al., 2007) and α5–integrin has been identified as a ligand for L1CAM-mediated chemoresistance (Sebens Müerköster et al., 2009). This chemoresistance was seen in response to drugs exerting different modes of action such as gemcitabine and etoposide indicating a broad protection against drug-induced apoptosis through L1CAM-mediated alterations in cell signalling and gene expression. Thus, interaction of α5-integrin and L1CAM led to an increased activity of the inducible nitric oxide synthase (iNOS) and subsequent increased release of nitric oxide (NO) resulting in the inhibition of caspases. In addition, interaction of α5-integrin and L1CAM led to constitutive activation of NF-κB via an increased production and secretion of IL-1β (Kiefel et al., 2010) which both are likewise important mediators of chemoresistance in PDAC cells (Arlt et al., 2002; Arlt et al., 2003; Müerköster et al., 2003). Stoeck et al. also demonstrated that L1CAM in its membrane-bound as well as in its soluble form confers apoptosis resistance in ovarian carcinoma cells towards C2-ceramide, staurosporine, cisplatin and hypoxia. Long-term treatment with the cytostatic drug cisplatin increased L1CAM expression level in ovarian carcinoma cells m130 (Stoeck et al., 2008) which was similarly observed in PDAC cells after long-term incubation with etoposide indicating a role for L1CAM in the acquired chemoresistance of tumor cells (Sebens Müerköster et al., 2007). Immunohistochemical analyses of pancreatic tissues together with data from coculture experiments indicate that L1CAM is not only upregulated during chemotherapy but also under the influence of the cellular microenvironment. Thus, L1CAM was upregulated in the pancreatic ductal epithelial cell line H6c7 when cultured in the presence of activated fibroblasts/myofibroblasts resembling the situation of a chronic pancreatitis (Geismann et al., 2009). Again elevated L1CAM expression conferred an apoptosis resistant phenotype

even in non-tumorigenic pancreatic epithelial cells. Recent data by Min et al. similarly showed that L1CAM diminished the apoptotic response of cholangiocarcinoma cells towards drug treatment with gemcitabine (Min et al., 2010). In glioblastoma stem cells, a role for L1CAM in the control of DNA damage checkpoint responses and resistance to radiotherapy has been described (Cheng et al., 2011). Radioresistance was mediated by nuclear translocation of L1CAM and subsequent regulation of NBS1 expression which is part of the MRE11-RAD50-NBS1 (MRN) complex and involved in early checkpoint responses. Since L1CAM has been identified as a marker for glioma stem cells being important for tumor formation in vivo (Bao et al., 2008), targeting of L1CAM might be a strategy to eliminate therapy-resistant tumor stem cells that are presumably responsible for therapy relapses.

Overall, all these findings underscore the importance of L1CAM in protection from apoptosis which might i) imply a survival advantage for genetically altered cells during tumorigenesis thereby promoting tumor formation and ii) explain the profound innate and acquired chemo- (radio-)resistance of therapy resistant tumors such as PDAC.

5. L1CAM as target structure in cancer treatment – preclinical results

The soluble form of L1CAM was not only detected in culture medium of several tumor cell lines (Fogel et al., 2003; Gavert et al., 2005; Gavert et al., 2007; Gutwein et al., 2005; Yang et al., 2009) but also in serum and ascites of uterine and ovarian carcinoma patients being associated with poor prognosis (Fogel et al., 2003; Gutwein et al., 2005). In contrast, a first screening of serum samples from patients with chronic pancreatitis or PDAC did not reveal elevated levels of soluble L1CAM (unpublished observations) indicating that soluble L1CAM plays only a minor role in pancreatic tumorigenesis. Accordingly, cell culture experiments revealed no effect of sheddase inhibitors in PDAC cells with regard to chemoresistance and EMT (Sebens Müerköster et al. 2007). However, detection of soluble L1CAM in serum for diagnostic and predictive purposes would allow a viable screening without exposing patients to expensive and troublesome interventions. To validate the specificity of elevated L1CAM ectodomain levels as a tumor serum marker, further screenings of serum samples from patients at earlier tumor stages and also with other diseases (e.g. inflammation) that may lead to upregulation and shedding of L1CAM are required.

The fact that tumoral L1CAM expression is often associated with an advanced tumor stage, metastasis and poor clinical outcome strongly suggests its suitability as a predictive marker in malignancies such as PDAC. In view of its multiple functions in tumor development and progression as well as its prevailing expression in tumors compared to normal tissues, L1CAM represents a promising target structure in anti-cancer therapy. This notion is substantially supported by several preclinical studies using anti-L1CAM antibodies or strategies based on genetic interference. Biweekly treatment with the anti-L1CAM antibody L1-11A dose-dependently inhibited tumor growth of intraperitoneally inoculated SKOV3ip ovarian carcinoma cells and ascites formation by up to 75 % in nude mice (Arlt et al., 2006). In the same tumor model system, therapeutic efficacy of L1CAM antibodies with different isotypes has been evaluated demonstrating that therapy with the L1-9.3/IgG2a antibody results in the best anti-tumor response in terms of reduced tumor burden and prolonged survival (Wolterink et al., 2010). Expression profiling of mRNA isolated from tumors

revealed an altered gene expression after L1CAM antibody treatment including genes involved in apoptosis, chemotaxis, angiogenesis and inflammatory responses. Moreover, antibody-treatment caused a massive infiltration of macrophages into the tumor suggesting that efficacy of anti-L1CAM antibody therapy is based on immunologically and non-immunologically mediated mechanisms (Wolterink et al., 2010). Therapeutic efficacy of radiolabeled anti-L1CAM antibodies has been proven in nude mice orthotopically inoculated with SKOV3ip ovarian carcinoma cells or with neuroblastoma xenografts (Hoefnagel et al. 2001; Knogler et al., 2007). Furthermore, it was demonstrated that mutation of the anti-L1CAM antibody chCE7 led to improved blood clearance and a single 10.5 MBq dose of ^{67}Cu-labeled mutated chCE7 antibody reduced tumor growth and prolonged survival of the mice (Knogler et al., 2007). Min et al. demonstrated in a nude mouse model with subcutaneously inoculated cholangiocarcinoma Choi-CK cells that treatment with an anti-L1CAM antibody three times per week resulted in reduced tumor outgrowth compared to therapy with a control antibody. Similar results were obtained with the cholangiocarcinoma cell line SCK in which L1CAM expression was suppressed by short hairpin RNA (shRNA) (Min et al. 2010). Targeting of L1CAM using lentiviral-mediated shRNA interference in glioma tumor stem cells before injection into nude mice reduced tumor formation and prolonged survival of tumor bearing mice as well (Bao et al., 2008).

Overall, these data highlight the importance of L1CAM in tumor growth and development and the suitability of L1CAM as therapeutic target in anti-cancer therapy. Nevertheless, it has to be critically stated, that in all of the above mentioned studies, antibody treatment started 2 to 3 days after tumor cell inoculation which does not reflect the clinical conditions of a high tumor load in advanced tumor patients but rather the situation of micrometastatic spread.

The fact that even in these models no complete cures were achieved by L1CAM antibody treatment alone points to the need of appropriate combination therapies. In particular for highly malignant tumors such as PDAC, therapeutic targeting of L1CAM alone will not be an effective therapy for cure. Hence, therapeutic strategies combining L1CAM targeting and chemo- or radiotherapy might act synergistically and lead to improved anti-tumor responses. This approach was followed by our group to provide an improved therapy for PDAC. In a SCID mouse model with subcutaneously grown Colo357 tumors, combined treatment with 10 mg/kg anti-L1CAM antibodies (L1-14.10 or L1-9.3/2a) and gemcitabine significantly reduced tumor growth compared to treatment with chemotherapy alone or in combination with control antibodies. This stronger anti-tumor effect could be attributed to an increased number of apoptotic tumor cells along with a reduced tumor vascularization and increased macrophage infiltration (unpublished observation). These data are in line with the findings from Wolterink et al. and suggest that the L1CAM antibody-mediated anti-tumor effect might not only rely on interference with L1CAM-mediated signalling in the tumor cells but also on the induction of anti-tumor immune reactivity. Combined treatment with L1CAM antibodies and chemotherapy has been proven to be an effective anti-tumor therapy also in other tumor models (unpublished observation).

Certainly, these subcutaneous tumor models do not reflect the pathological conditions of PDAC and are therefore limited in their clinical significance. Addressing this issue we used a SCID mouse tumor model with H6c7 cells that were intrapancreatically co-inoculated with pancreatic myofibroblasts (PMFs) (see above). Whilst H6c7 cells inoculated without PMFs

did not produce measurable tumors and metastases, PMF co-inoculated H6c7 cells became highly tumorigenic leading to the formation of primary, stroma enriched tumors in 88% and to liver metastases in 75 % of the inoculated mice, as determined by high-resolution ultrasound. Intriguingly, treatment of these already tumor-bearing mice with 10 mg/kg of the anti-L1CAM antibody L1-9.3/2a resulted in a complete tumor remission and reduced formation of liver metastases in 50 % of the animals (unpublished observation).

6. Conclusions

Originally identified in the nervous system, L1CAM has meanwhile been detected in numerous cancers including PDAC. Aberrant expression of L1CAM in tumors has been identified to be a key player in tumor formation, progression and metastasis. PDAC is also characterized by elevated L1CAM expression in the primary tumor as well as in metastases. The fact that upregulation of L1CAM expression occurs already in PDAC precursor lesions such as PanINs and chronic pancreatitis strongly favours its involvement in pancreatic tumorigenesis. Accordingly, several studies demonstrated a pivotal role of L1CAM in tumor cell migration, survival and chemoresistance of PDAC cells. In view of its broad impact in PDAC progression and its favourably restricted expression in adult tissues, L1CAM represents a promising target to improve treatment of PDAC. Moreover, results from preclinical studies demonstrating that antibody-mediated targeting of L1CAM significantly ameliorated the efficacy of chemotherapy in PDAC cells and resulted in improved anti-tumor responses give rise to optimism. Hence, these findings should be validated in clinical studies and at the same time we have to continue to deepen our understanding on the mechanisms by which L1CAM impacts on tumor cell biology. Targeting of L1CAM alone will definitely not be effective enough in eliminating highly malignant tumors such as PDAC but it rather provides an appropriate therapeutic tool for combined treatment. In this context, more work and efforts are still needed to identify the most effective combination of therapeutic strategies.

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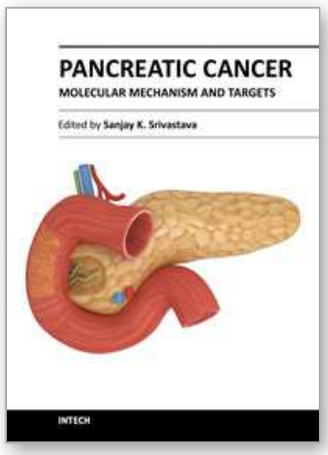

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This book provides the reader with an overall understanding of the biology of pancreatic cancer, hereditary, complex signaling pathways and alternative therapies. The book explains nutrigenomics and epigenetics mechanisms such as DNA methylation, which may explain the etiology or progression of pancreatic cancer. Book also summarizes the molecular control of oncogenic pathways such as K-Ras and KLF4. Since pancreatic cancer metastasizes to vital organs resulting in poor prognosis, special emphasis is given to the mechanism of tumor cell invasion and metastasis. Role of nitric oxide and Syk kinase in tumor metastasis is discussed in detail. Prevention strategies for pancreatic cancer are also described. The molecular mechanisms of the anti-cancer effects of curcumin, benzyl isothiocyante and vitamin D are discussed in detail. Furthermore, this book covers the basic mechanisms of resistance of pancreatic cancer to chemotherapy drugs such as gemcitabine and 5-flourouracil.

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