

Review

CD15 and CD15s in the Anticancer Therapy

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Simple Summary: CD15 antigen is found on various cancer cells, including renal cancer, prostate and bladder cancers, acute leukemias, hepatocellular carcinoma, breast cancer and melanoma. Its high expression serves as a good prognostic marker for patients and high hopes are related to its use in the immunotherapy of the tumor. CD15 interacts with E-, L- and P-selectins, which allows for the adhesion with the endothelial cells and consequently to metastases. The blockage of antigen's function results in reduced metastatic potential. It may be an immunotherapeutic target against cancer. CD15s is a sialyl derivative of CD15, however, unlike the high expression of CD15 which is a prognostic factor in Hodgkin lymphoma, CD15s relate to poor prognosis for the patients. CD15 is considered as a marker of cancer stem cells. This review presents a comprehensive description of the role of CD15 and CD15s in the anticancer therapy.

Abstract: CD15 (Lewis X/Lex) is a fucosyl (3-fucosyl-N-acetyl-lactosamine) moiety found on membrane proteins of various cancer cells. These include renal cancer, prostate and bladder cancers, acute leukemias, hepatocellular carcinoma, breast cancer and melanoma. The antigen plays an especially significant role in renal cell carcinoma. Its high expression serves as a good prognostic marker for patients and high hopes are related to its use in the immunotherapy of the tumor. The biological role of CD15 is the interaction with E-, L- and P-selectins (adhesion molecules) and allowing for the adhesion with the endothelial cells. In this way, cancer cells start to interact with the endothelium of blood vessels and consequently move out from the blood flow to the surrounding tissues. The blockage of antigen's function results in reduced metastatic potential. Moreover, the molecule may be a therapeutic target against cancer in monoclonal antibodies-based therapies. CD15s is a sialyl derivative of CD15, that possess its own unique characteristics. Unlike high expression of CD15, which is a prognostic factor in Hodgkin lymphoma, CD15s relate to poor prognosis for the patients. Due to the high abundance in cancer cells, CD15 is considered as a marker of Cancer Stem Cells. This review presents a comprehensive description of the role of CD15 and CD15s in cancer development and metastasis and overviews the clinical applications of the anti-CD15 therapy.

Keywords: CD15, Lewis X, Lex, Cancer, Therapy

1. CD15 and CD15s function

CD15 (Lewis X) is a typical myeloid antigen found on the myeloid and monocytic lineages of cells. Depending on the cell origin, the expression of the antigen is determined by different isoforms of α 1,3-fucosyltransferase. For instance, in mature granulocytes, it

is the IX isoform, whereas in promyelocytes or monocytes, it is isoform IV [4]. Classically, the antigen was used to distinguish between Hodgkin (positive) and non-Hodgkin lymphomas. Curiously, its expression pattern is not fully restricted to Hodgkin lymphoma, but also to peripheral T-cell lymphomas and primary cutaneous anaplastic large cell lymphoma [2]. Moreover, the antigen is widely expressed among immature cells, including a range of CNS progenitors [6]. Curiously, the aberrant expression of CD15 was observed among various tumors. Not only were hematological malignancies stained positive for CD15, but also several solid tumors overexpressed CD15. In general, tissues with high content of hyaluronic acid seem positive for CD15 stain due to the high level of glycan content [7]. Besides, adenocarcinomas express high levels of CD15 [2]. Various studies aim to correlate the expression of the molecule with the potential of tumor progression and survival of the patient. Further paragraphs present the role of CD15 in renal neoplasms and the therapeutical approaches by targeting the antigen.

CD15 acts as a ligand for selectins in the transendothelial migration. The molecule allows for the adhesion of the cell to the blood vessel endothelial cells and the recruitment of the circulating cells from the blood flow [8]. Further, the cytokines such as $\text{TNF}\alpha$, IL-6 or IL-1 β activate the CD62E (E-selectin) [9]. The molecules allow for the tighter adhesion of the endothelial cells with the cell from blood flow. In the next step, the cell may migrate between the endothelial cells [10]. The process is especially important in case of tumor metastasis [11].

Aside from its role in cancer metastasis, CD15 is also abundant on normal cells and considered as the marker of myeloid cells. The molecule mediates the neutrophil adhesion to dendritic cells [12]. CD15 also serves as a marker of granulocytes [13]. The antigen is also critical in the fetal development of the central nervous system. CD15 may be found in the interganglionic boundary (from the sulcus interstriatus to an area of the ventral margin of the caudate nucleus) [14].

2. Role of CD15 and CD15s in neoplasms

Significant changes of the cell surface carbohydrates were proved to accompany neoplastic transformation and they seem to be associated with tumour invasiveness and metastatic behaviour [15,16]. Overexpression of both CD15 and CD15s can be found on the surface of various types of cancer cells [17–20]. Elevated CD15 is associated with the adhesion of some cancer cells during the metastasis process since CD15 located on cancer cells can bind by homophilic interaction with CD15 located on vascular endothelial cells. This process starts a heterophilic interaction with other cell adhesion molecules, including those of the selectin family – consisting of E-, L- and P- selectin. It was demonstrated that CD15 and CD15s play an important role in the adhesion of cancer cells to the endothelium of blood vessels [21–24]. For reference, see figure 2. P-selectin and E-selectin are located on the surface of the endothelial cells. The initial step of cell adhesion (tethering), between CD15s and E-selectin, is crucial for cancer metastasis [25,26]. Furthermore, researchers established CD15s to be the specific ligand of L-selectin, which in turn is constitutively expressed on leukocytes [27]. This results in a binding of leukocytes and cancer cells, which facilitates metastatic spread via the circulatory system. Another mechanism involving CD15 and CD15s in malignancies progression is their ability to change the structure of membrane-bound proteins (e.g. mucins), which may hide cancer cells from being destructed by NK cells [28]. Multiple studies discussing the role of CD15 and CD15s in cancer pathogenesis and prognosis have been published so far.

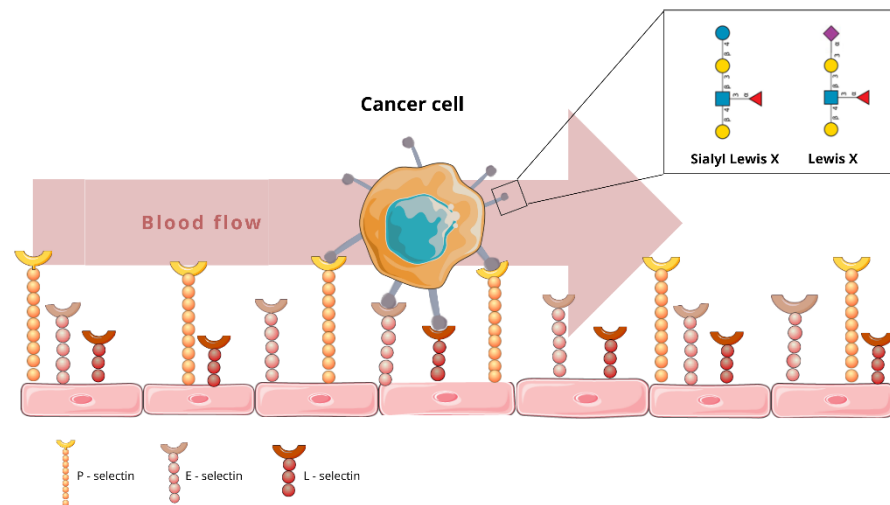


Figure 2. Cancer cell adhesion to the endothelial cells by the Lewis X antigen interacting with E-, L- and P-selectins. The figure presents the first step in the transendothelial migration of cancer cells.

Nakagoe et al. analysed the expression of CD15s in a cohort of 101 patients with 0-II stage gastric cancer who underwent curative gastrectomy to clarify its prognostic value [29]. In 31 patients, a high expression of CD15s antigen within their tumours was detected. These patients had shorter disease-free intervals ($p < 0.0001$) and worse disease-specific survival (HR 9.1 for high CD15s expression) than those with negative or low CD15s expression. The authors concluded that CD15s might serve as a prognostic factor in 0-II stage gastric cancer. Futamura et al. examined immunohistochemically the expression of CD15s in 245 patients with gastric cancer, which resulted in 135 (55%) positive cases [30]. Moreover, the occurrence of lymph nodes invasion, liver metastasis and stage III/IV tumours were significantly higher in CD15s-positive patients than in CD15s-negative ones ($p < 0.01$, $p < 0.01$, $p = 0.028$, respectively). The overall prognoses were also worse for patients with high CD15s expression ($p = 0.019$). An elevated expression of CD15 on gastric epithelial cells seems to be correlated with intestinal metaplasia, the precursor of gastric cancer [31].

Opposite changes were observed in oesophageal adenocarcinoma developed in Barret's epithelium, in which the expression of CD15 was reported to be much lower than in non-Barret's cancer [32]. However, the study cohort consisted of only 50 patients (17/50 Barret's adenocarcinoma), which may affect the reliability of the results. These observations seem to find confirmation in the study of Faried et al., who demonstrated high expression of CD15 in 31% of patients (40/130) with oesophageal squamous cell carcinoma (non-Barret's cancer) [33]. The authors found a strong correlation between occurrence of this antigen and worse TNM classification ($p < 0.01$), lymph node metastasis ($p < 0.0001$) and blood vessel invasion ($p < 0.0001$). The overall 5-year survival rate of these patients was significantly lower than the patients who were CD15-negative (10% vs. 66%, respectively, $p < 0.0001$).

The prognostic values of CD15 and CD15s in colorectal cancer have been fairly well documented over the years. The 5-year disease-free survival rates in a group of 132 patients were 58% and 89% for patients with CD15s-positive and CD15s-negative tumours, respectively ($p < 0.001$) [34]. Differences in the 5-year overall survival rates in this group were also significant – 58% for CD15s-positive and 93% for CD15-negative patients ($p <$

0.001). Another study of 120 patients with colorectal cancer, of which 87 (72.5%) had high expression of CD15s, also resulted in a statistically significant difference between overall 5-year survival of CD15s-positive and CD15s-negative patients (61% vs. 81%, $p < 0.05$) [35]. Grabowski et al. divided 182 patients with colon cancer into 2 groups based on the CD15s expression intensity on the carcinoma cells, assessing the UICC stage [36]. Strong CD15s expression was detected in 103 patients, while weak in 79 patients. Strong expression of CD15s was associated with a reduction of the 5-year overall survival rate in UICC stage II (54% vs. 84%, $p < 0.01$) and stage III patients (35% vs. 86%, $p < 0.01$). Taking the value of CD15s expression in colorectal cancer into consideration, in 2012, Schiffmann et al. established a new scoring system as an easy tool to assess CD15s expression intensity [37]. Several studies aimed to determine the prevalence of CD15 on colorectal cancer cells and non-lesion, healthy colon cells. Shi et al. in one of the very first trials on this topic demonstrated CD15 expression in 100% of colonic adenocarcinoma tissues examined [20]. However, the cohort included only 20 cases. In a more recent study, Portela et al. reported CD15s in 75% of colorectal cancer samples, while in only 6.7% of healthy colon tissue samples obtained from the same patients [38]. Lastly, Jang et al. published the results of performing immunohistochemical staining for CD15 in 42 cases of colorectal carcinoma, 49 of tubular adenoma, 15 of hyperplastic polyp, and 17 of the non-neoplastic colon [39]. The CD15 expression level was significantly higher in colorectal carcinoma (48%) than in low grade tubular adenoma (23%), hyperplastic polyp (0%) and non-neoplastic colon (6%) ($p < 0.05$). Furthermore, the CD15 expression was shown to increase during cancer development and progression progressively.

Hepatocellular carcinoma (HCC), the primary malignant disease of the liver, is different from other solid tumours because it is commonly associated with the occurrence of intrahepatic metastasis, which is a poor prognostic factor [40]. There is a correlation between CD15 expression and intrahepatic metastasis – 69% vs. 30% ($p < 0.02$) occurrence in patients with CD15-positive HCC and CD15-negative HCC, respectively, although the difference in survival rate is not statistically significant [41]. The CD15s expression in liver tissue was found to be not specific for HCC, the study of Fujiwara et al. revealed expression of this antigen in 53% of chronic hepatitis tissue specimens and 89% of pre-cirrhotic and cirrhotic tissue specimens [42]. Nevertheless, all of the HCC specimens had positive CD15s expression. Okada et al. observed either membranous or cytoplasmic expression of CD15s on HCC cells. The cytoplasmic-positive cells were well differentiated, while membrane-positive were less differentiated. Moreover, the authors demonstrated a positive correlation between tumour size and CD15s expression [43].

CD15 was shown to be a sensitive and specific marker of bile duct neoplasms; therefore, it may become the potential novel tool to differentiate dysplastic and neoplastic biliary cells from non-neoplastic tissue, which is a common diagnostic problem in indeterminate biliary stricture [44]. Kashiwagi et al. detected CD15s not only in gallbladder cancer cells cytoplasm (52%, 28/54) but also in cancer stroma (39%, 21/54) [45]. Stromal expression of CD15s was frequently associated with lymphatic invasion, venous invasion and lymph node metastasis (54%, 50% and 60%, respectively, $p < 0.05$), which are known factors of poor prognosis.

In the study of Fukushima et al., out of the 92 lung cancer samples examined, CD15 and CD15s were detected in 42% (39 cases) and 57% (52 cases) [19]. Higher expression was seen in the 54 lung adenocarcinomas – CD15 in 48% (26 cases) and CD15s in 72% (39 cases). These results indicate that CD15s are a useful marker for lung adenocarcinomas. An important problem in the lung cancer diagnosis is to distinct peripheral lung adenocarcinoma involving the pleura from pleural epithelial mesothelioma. Comin et al. found CD15 the most specific marker in differentiating mesotheliomas from adenocarci-

nomas – only 4.5% of mesothelioma cases, while 100% of adenocarcinoma cases expressed CD15 [46]. Mizuguchi et al. analyzed the clinical significance of serum CD15s concentrations as a predictor of lymph nodes metastasis, based on 272 patients with non-small-cell lung cancer who underwent pulmonary resection [47]. The median CD15s serum concentrations were 44 U/mL for N2/N3 patients and 27 U/mL for N0/N1 patients. The 5-year survival rates of patients with concentrations of CD15s > 38 U/mL and those with lower concentrations were 32% and 69%, respectively ($p < 0.0001$), which suggests the potential usefulness of serum CD15s concentrations as a staging marker and predictor. Likewise, CD15s expression on the surface of lung cancer cells was linked with a higher probability of post-operative distant metastasis and shorter overall survival [35]. Martín-Satué et al. proved the crucial role of CD15s in a lung adenocarcinoma metastasis process [21].

Another malignancy is confirmed to express CD15 antigen on the surface of its cells in breast cancer [48,49]. Similarly to lung adenocarcinoma, CD15 and CD15s are established key antigens in breast cancer progression and metastasis, enabling endothelial adhesion [18]. Sozzani et al. aimed to evaluate the prognostic value of CD15s in a long-term follow-up study and the results were different than for other cancers [50]. A total of 127 consecutive patients with primary breast cancer were included in the trial. The median follow-up time was 140 months. CD15s antigen expression was found in 37 specimens (21%). The overall survival and disease-free survival were similar for CD15s-positive and CD15s-negative patients (62% vs. 60% and 59% vs. 56%, respectively). The expression of CD15s seems to be not associated with breast cancer survival.

Hodgkin's lymphoma was one of the first malignancies with demonstrated CD15 expression. In the 1980s, the Hodgkin-Reed-Stenberg (HRS) cells were found to react with the LeuM1 antibody raised against CD15 antigen [51]. The detection of CD15 on HRS cells has been used as a diagnostic marker of Hodgkin's lymphoma for years [52]. Researchers found the expression of CD15 on HRS cells as a favorable prognostic factor, while the expression of CD15s was correlated with poor prognosis [18,53]. Although the expression of CD15 is not entirely specific for HRS, it is rather sensitive - detected in approximately 80% of all classical Hodgkin's lymphomas [54].

Finally, the expressions of CD15 and CD15s were identified in urological malignancies. Sheinfeld et al. performed an immunohistochemical analysis which demonstrated that CD15 is not detected in normal adult urothelium except for occasional umbrella cells [55]. Nevertheless, the expression was identified in 100% of invasive urothelial cell carcinomas and 78% of carcinoma in situ cases, regardless of grade, stage, blood type or secretor status, which is in line with other studies [56]. The presence of CD15-positive cells in bladder specimens enhanced the detection of urothelial tumours, correctly identifying bladder cancers in 253/293 (86%) cases compared to 63% for cytology alone [55]. A recently published study by Ezeabikwa et al. resulted in intriguing disclosure that CD15 is highly expressed on low-grade bladder cancer cell lines. In contrast, high-grade cell lines were associated with low or lack of expression (on normal bladder epithelial CD15 was not expressed at all) [57]. Numahata et al. found CD15s expression in 70% urothelial bladder carcinomas and correlated it with lymph node invasion, blood-borne metastasis and a lower 5-year survival rate [23]. Researchers investigated the value of different urine markers in bladder cancer, which resulted in 86% median sensitivity (80-94%) and 73% median specificity (37-86%) for CD15 [58-61]. However, the sensitivity, with the median of 75% (68-79%), was worse in recurrent disease, while the median specificity increased to 82% (67-86%). CD15 was concluded in the systematic review to be one of the most promising urine markers of bladder cancer [62].

Overexpression of CD15 and CD15s antigens were also demonstrated in prostate cancer [63,64]. The upregulation of CD15s is associated with hormonal-resistant, aggressive disease [63]. High expression of CD15 and CD15s may influence prostate cancer progression through several mechanisms, including immune recognition by selectins or modifications of prostate cells mucins that enable cancer cells to evade destruction by NK cells [28]. In a recent study, CD15s expression on prostate cancer cells was found to be regulated by androgens [65]. This may be one of the factors why androgens play a crucial role in the development and progression of prostate cancer, and why androgen deprivation therapy is usually the first-line treatment in metastatic disease.

In 2016 Liang et al. performed a meta-analysis of 29 studies to establish the relationship between CD15s expression on the surface of malignant cells overall, cancer prognosis and clinicopathology [66]. It concluded that a high level of CD15s expression is significantly associated with lymphatic invasion, venous invasion, deep invasion, lymph node metastasis, distant metastasis, tumour stage, tumour recurrence and overall survival in cancer overall. The authors suggested CD15s as a new diagnostic and prognostic biomarker with the potential to become a therapeutic target in different types of cancer. Nevertheless, further studies are required to investigate the factors that caused significant heterogeneity in this meta-analysis.

3. Role of CD15 and CD15s in RCC

Despite all the findings above, proving diagnostic and prognostic values in many cancers, the role of CD15 and CD15s antigens in RCC is still unclear and insufficiently studied. Several researchers confirmed the expression of these antigens on the surface of RCC cells [67–70]. However, their influence on RCC progression and prognosis is more controversial and complex than in other cancers.

One of the first trials to investigate the presence of CD15 in RCC was enrolled by Cordon-Cardo et al. in the late 1980s [67]. It resulted in 76% (22/29) of CD15-positive specimens. Interestingly, the authors also analysed samples of 15 metastatic tumours, finding CD15 overexpression on occasional cells in only 20% of cases. Despite a small cohort, the percentage obtained is in line with more recent studies. Røge et al. based on 109 patients with different RCC types reported CD15 expression in approximately 80% of cases, while Ordóñez et al. in 63% of 48 patients [68,69]. RCC cells were shown to express CD15 varying to subtype. Pan et al. reported such results based on the biggest cohort so far (328 cases) [70]. CD15 expression was found on 62% of clear cell RCC (ccRCC), 41% of papillary RCC and 11% of chromophobe RCC. The results were similar to findings of López et al. (130 cases), who demonstrated the expression in 60% of ccRCC, 56% of papillary RCC and 0% of chromophobe RCC [71]. The presented values seem to be lower than CD15 expression in RCC overall. Nevertheless, the difference may be made up by more recent results - Røge et al. found CD15-positive cells in 77% of ccRCC and 85% of papillary RCC (there were only 13 papillary RCC cases), while Wu et al. reported the expression in 246/301 (82%) of ccRCC cases [68,72]. Several studies also found CD15 antigens on the proximal tubules of normal kidneys [67,72,73]. The CD15 expression on RCC cells may have clinical value itself. CD15 is considered as one of the best markers to distinguish between RCC lung or pleura metastasis and mesothelioma, two malignancies presenting a wide variety of morphological patterns, confusing clinicians [69]. However, the conclusion is inconsistent with the previously cited Cordon-Cardo et al. findings of CD15 overexpression in metastatic tumours and needs further analysis [67]. Recently, CD15 prognostic value in ccRCC was demonstrated based on the biggest sample size so far [72]. Authors associated loss of CD15 expression with lymphatic invasion, vascular invasion, necrosis, higher tumour grade, and a reduction of the 5-year overall survival rate from 37% to 26%. It was speculated that loss of CD15 expression indicates a

poorer prognosis due to decreased ccRCC cell differentiation. In conclusion, CD15 expression is a good prognostic factor in ccRCC, although more data is needed to get convincing findings.

The influence of CD15s on prognosis in RCC is debatable and so far, presented results were contradictory at first glance. Nevertheless, the authors were in line with CD15s overexpression in RCC. Koga et al. investigated the metastatic potential of RCC by intravenously injecting mice with four lines of human RCC cells [74]. One line had a significantly higher ability to produce pulmonary metastatic nodules, while the rest produced either few or no metastatic nodules. A flow cytometric analysis revealed that only this cell line demonstrated high CD15s expression. This finding indicates that CD15s possibly plays a critical role in the hematogenic metastasis of RCC. However, in the first trial on the human cohort, Fukushi et al. found CD15s expression as the factor of good prognosis [35]. The authors of this study used FH6 monoclonal antibodies for CD15s detection. The interaction was positive in 47% of RCC samples. On the other hand, Tozawa et al., who used CSLEX1 monoclonal antibody for CD15s detection, demonstrated CD15s expression to be the factor of poor prognosis [75]. The expression overall was found in 100% of examined cases, but higher expression intensity was correlated with higher tumour stage and grade, lymph node invasion, vascular invasion, metastasis and shorter tumour-free survival. In the most recent study, Kobayashi et al. used both FH6 and CSLEX1 monoclonal antibodies to explore the capacity of expression of CD15s antigen as a predictor of prognosis in 52 RCC cases [76]. The expression was positive for FH6 and CSLEX1 monoclonal antibodies in 54% (28/52) and 71% (37/52) of specimens, respectively. The expression status of CD15s in total did not impact disease progression or overall survival rate. However, CD15s antigens recognized using FH6 and those using CSLEX1 seemed to negatively affect disease progression and prognosis. Those detected by FH6 were suggested as the good prognosis factor, while by CSLEX1 as the poor prognosis factor. The authors concluded that the combined use of FH6 and CSLEX1 monoclonal antibodies is a powerful predictor of patients with unfavourable prognosis – those with CD15s expression of low FH6 and high CSLEX1. These monoclonal antibodies were found to react with different glycolipids. Moreover, it was shown that the sugar determinant of CD15s varies depending on the tissue origin. Therefore, it might be the explanation why the interaction between CD15s sugar determinant of RCC and theoretically two CD15s-specific monoclonal antibodies were different and why the results of the aforementioned studies were initially opposite. However, more studies about the role of both CD15 and CD15s are required.

4. Experimental medicine involving CD15

Due to the important role of the CD15 in cancer metastasis, the molecule is nowadays considered as a potential target for cancer immunotherapy. Various drugs try to modulate both the expression of CD15 and E-selectin to disallow for the cell adhesion to the endothelium and prevent the metastatic process.

Several cancers have demonstrated the expression of CD15. These include papillary thyroid carcinoma, Hodgkin's lymphoma, non-small-cell lung cancer, oral cancer, glioma and breast cancer. Each neoplasm differed in the expression of the antigen and thus the prognosis for the patient and the response to the therapy.

For the first time in 2019 was provided that the expression of CD15, which is one of the cancer stem cells markers is associated with patient prognosis in papillary thyroid carcinoma (PTC). There was conducted immunohistochemical staining of CSC markers in constructed tissue microarrays from PTC samples. The obtained results show that CD15 expression is associated with shorter progression-free survival (PFS) [77].

Great example was presented by Elola et al., who showed a promising attempt of preventing breast cancer cells metastasis by targeting the interaction between CD15 and adhesion molecules on endothelial cells [17]. The authors incubated MCF-7 breast cancer cells with HUVEC cells and analyzed the interaction of both cell types following the incubation with mAbs against CD15. They revealed that mAbs might lyse the interaction between the cells and thus prevent from the spreading of cancer cells through the vessels. Based on the in vitro research, the authors proposed a model for preventing cancer metastasis by targeting CD15 [17]. 5% of patients with breast cancer (BC) suffer from infiltration of the leptomeninges by metastatic carcinoma also known as leptomeningeal carcinomatosis [78]. Circulating tumour cells (CTCs) appear in the blood as well as in cerebral spinal fluid (CSF) patients with breast cancer (BC) leptomeningeal metastasis (LM) [79]. In the 2017 experiment, CSF samples from patients with BCLM were analyzed using flow cytometry. For the first time, there was demonstrated CD15 overexpression in CSF cancer floating cells. It allows concluding CD15 as a potential prognostic biomarker of risk breast cancer metastasis, poor prognosis and tumour recurrence [80]. Another research was conducted on MCF-7 cell line in subject of the anticancer therapy using the IgM mAbs. Mordoh et al. proved that FC-2.15 mAbs against CD15 mediate the complement cytotoxicity against tumor and reduces the clonogenic capacity. Besides, the studies showed the selectivity of the antibodies against cancer cells with no effect on the normal bone marrow cells [48]. Besides, in human lung adenocarcinoma cells, CD15s are involved in the adhesion process and by targeting the antigen we might decrease the metastatic potential of the cells [21]. Tozawa et al. found an interesting side effect of cimetidine for patients suffering from RCC. Namely, the drug suppresses the expression of E-selectin on vascular endothelial cells, thus disallowing the adhesion and migration of cancer cells. The study suggests, that cimetidine may inhibit the metastatic process in patients with RCC [75]. Jiang et al. proved that the adhesion of the gastric cancer cells to endothelium may be inhibited by andrographolide. The molecule blocks E-selectin expression and thus disallows for adhesion via the CD15-E-selectin contact. When cells treated with andrographolide are preincubated with E-selectin and CD15, the effect of the andrographolide nullifies [81]. Moreover, S-nitrosocaptopril (CapNO) inhibits CD15s expression in HT29 cell line. Lu et al. proved that the drug may be used for cancer metastatic chemoprevention [82].

Androgen deprivation therapy (ADT) acts on CD15 antigen via the modulation of androgen receptors. The latter regulates the biosynthesis of associated glycans, such as sialyl-Tn, CD15, chondroitin sulfate and O-GlcNAc. Therefore, Munkley proved that ADT induces the modification of prostate cancer traits related to glycans on their cell membranes [65].

Proper diagnosis of Hodgkin's lymphoma involves the identification of Reed-Sternberg cells (RSC) in biopsy specimens. They are located in a rich background composed of cells such as lymphocytes, eosinophils, and histiocytes, which make them difficult to find [83]. CD15 can be used for the fine-needle aspiration cytology (FNAC) identification of RSC. Cytopathological expression of CD15 occurs in 66,7% of cases. In addition, CD15 resulted to be more effective on smears and cell blocks [84]. CD15 can also be detected as being stained using autoclave and microwave. The positivity in the microwave test is 92% and in an autoclave is 50% [85]. Anti-CD15 antibodies were also introduced in the therapy of AML in Phase I clinical trial [86].

Approximately 85% of patients with lung cancer have non-small-cell lung cancer (NSCLC) and 20-40% of these patients can develop brain metastasis [87,88]. There was proven using three different methods and four human cancer lines that fucosylated carbohydrate epitopes CD15 and sialylated CD15s have a role in the developing brain tumour. Disruption of cerebral endothelial cell monolayers and cancer cells adhesion to

the cerebral endothelial cells is increased by overexpression of these epitopes. These findings demonstrate that these epitopes can be possibly used as metastasis biomarkers [89].

Oxidized low-density lipoprotein (OxLDL) is in control of endothelial cells and macrophage foam cells. The main OxLDL receptor is the lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) [90]. Human polymorphonuclear-myeloid derived suppressor cells (PMN-MDSCs), which are involved in NSCLC progression, can be determined by LOX-1. Recently it was found that LOX-1+ CD15+ PMN-MDSCs increase immune suppression and promote tumour expression. LOX-1+ CD15+ PMN-MDSCs can be useful in prognosis and recurrence after the surgery. LOX-1+ CD15+ PMN-MDSCs proportion enhances in the case of NSCLC and recurrence. All these findings were detected using flow cytometry in the peripheral blood of patients with NSCLC and health controls [91].

Myeloid-derived suppressor cells (MDSC) were first described in 2007. They are a congregation of pathological myeloid precursors, activated due to a chronic inflammation caused by a growing tumour. MDSCs protect the tumour against the host immune system providing the suitable condition for its growth [92,93]. CD15+ MDSC is present in the tissue of oral cancer. Immunohistochemistry analysis of biopsy and resected specimens proved that decreasing its number due to preoperative chemotherapy can improve the prognosis [94].

Gliomas are the most common malignant primary tumours of the brain and spinal cord, stay mostly mortal. The experiment conducted in 2021 proves that differentiated glioma cells with high expression of CD15 in conditions of hypoxia undergo dedifferentiation into cancer stem cells. This study shows that CD15 can be a potential marker of malignant glioma progression [95].

5. Clinical trials targeting CD15

Several clinical trials revealed the expression of the CD15 molecule in pathology conditions. Antibody-based therapies analyze the changes in CD15 molecule on various cancer cells. These include metastatic RCC, non-small cell lung cancer, MDS, ALL, AML, melanoma and colon cancer. Non-cancerous conditions include pulmonary embolism and deep vein thrombosis. All the clinical trials are summarized in table 1.

Table 1. Clinical trials involving CD15 molecule

Patients Number	Condition or disease	Therapy Protocol	Target antigen	Short Description	Recruitment Status	Ref.
40	Metastatic Renal Cell Carcinoma, Renal Cell Carcinoma Associated With Xp11.2 Translocations/TFE3	cdDrug: Axitinib Biological: Nivolumab	CD15, CD45, CD11b, CD33, CD14, HLA-DR, CE4, CD3, CD24, FoxP3, CD8, CD69, CD38, PD1,	Axitinib/Nivolumab Combination Therapy vs. Single Agent Nivolumab for the Treatment of TFE/Translocation Renal Cell Carcinoma (tRCC) Across All Age Groups	Suspended (Other - Assess strategies to improve accrual rate)	NCT03595124

	Gene Fu- sions, Stage III Renal Cell Cancer AJCC v8, Stage IV Renal Cell Cancer AJCC v8, Unresec- table Renal Cell Carci- noma		CD244, TIM3, CD4			
350	Non-small Cell Lung Cancer	Drug: pem- broli- zumab + chemo- therapy	CD15,PD-L1, CD8, FoxP3, PD1, CD163,	Prediction of Re- sponse to Treatment with pembroli- zumab + Chemo- therapy in Non- Small Cell Lung Cancer	Recruiting	NCT045890 13
18	Deep Vein Thrombosis, Pulmonary Embolism, Cancer	Drug: Tin- zaparin	CD15, CD24, CA19-9, TF, VEGF, TEPI	Thromboprophylaxis for Patients Undergoing Surgical Resection for Colon Cancer (PERI-OP)	Completed	NCT009671 48
20	Myelodys- plastic Syn- dromes, MDS/MPN Crossover Syndromes	Drug: 5- azacyti- dineDrug: Decita- bine	CD15, CD11b, CD14	5-Azacitidine and Decitabine Epige- netic Therapy for Myeloid Malignan- cies	Recruiting	NCT041877 03

260	Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia, Myelodysplastic Syndrome	AlloHeme Test (ACROBAT)	CD15+, CD3+, CD33+, CD34+	Assessment of Chimerism and Relapse Post Bone Marrow/Hematopoietic Cell Transplant (HCT) Using AlloHeme Test (ACROBAT)	Not yet recruiting	NCT04635384
100	Colorectal Carcinoma	Procedure: Fasting	CD15, CD3, CD4, CD8, CD19, CD45RA, CD62L, CD25, CD127, CD14, CD16, CD56, CD11b	Short-term Fasting Effects on Chemotherapy Toxicity and Efficacy	Enrolling by invitation	NCT04247464
116	Acute Myeloid Leukemia	Drug: Transplants from 8/8-matched Unrelated donors Drug: Transplants from family-mismatched/haploidentical donors	CD15, CD33, CD3	Transplantation From Family-mismatched/Haploidentical Donors With Matched Unrelated Donors in Adult Patients With Acute Myeloid Leukemia	Unknown	NCT01751997
47	Advanced Melanoma, Recurrent Melanoma,	Biological: Pembrolizumab	CD15, PD-L1, PD-1, CD80, CD86, FoxP3, CD68, PG-M1, DAKO,	Talimogene Laherparepvec (TVEC) (NSC-785349) and MK-3475 (Pembrolizumab) (NSC-	Active, not recruiting	NCT02965716

	Stage III Cutaneous Melanoma AJCC v7, Stage IIIA Cutaneous Melanoma AJCC v7, Stage IIIB Cutaneous Melanoma AJCC v7, Stage IIIC Cutaneous Melanoma AJCC v7, Stage IV Cutaneous Melanoma AJCC v6 and v7, Unresectable Melanoma	Biological: Talimogene Laherparepvec	CD14	776864) in Patients With Advanced Melanoma Who Have Progressed on Anti-PD1/L1 Based Therapy		
200	Renal Cell Carcinoma, Clear-cell Metastatic Renal Cell Carcinoma	Biological: Nivolumab/Ipilimumab	CD15, HLA-DR, CD11b, CD14, CD33, FoxP3, CD25, CD45RA, CD127, slan, CD1c, CD11c, CD123, CD141, CD303, ICOS, PD-1, PD-L1, CTLA-4, CD27, CD28, CD45RA, CD45RO, CD57, CD95, CD69, CD25, CD107a,	Tailored Immunotherapy Approach With Nivolumab in Subjects With Metastatic or Advanced Renal Cell Carcinoma (TITAN-RCC)	Active, not recruiting	NCT02917772

TNF- α , IL-
4, IL 17, IL-
10,

6. Summary

CD15 proved itself to be a potent target for renal cancer therapy. By acting on both – cancer cells and immune myeloid-derived cells, the clinicians may obtain a higher response to the therapy and induce the changes in the tumor microenvironment that would not promote cancer growth and progression. Current urological attempts should aim to improve the clinical application of the anti-CD15 therapy and analyze the safety of the therapy. Otherwise, targeting CD15 and CD15s seemss to be an interesting treatment option, which is proved by successive experimental and clinical studies progress.

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