Nectins and Nectin-like Molecules in Colorectal Cancer

Subjects: Surgery
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In 2020, colorectal cancer was the third most common type of cancer worldwide with a clearly visible increase in the number of cases each year. With relatively high mortality rates and an uncertain prognosis, colorectal cancer is a serious health problem. There is an urgent need to investigate its specific mechanism of carcinogenesis and progression in order to develop new strategies of action against this cancer. Nectins and Nectin-like molecules are cell adhesion molecules that take part in a plethora of essential processes in healthy tissues as well as mediating substantial actions for tumor initiation and evolution.

Nectin Necl cancer colorectal diagnostics

1. Introduction

Colorectal cancer (CRC) is a serious worldwide health problem with over 1.9 million new cases estimated in 2020 [1]. Globally, CRC is the third most commonly diagnosed cancer in both sexes combined [2]. It is estimated that CRC is the second most common cause of cancer-related mortality and accounts for approximately 930 thousand deaths around the world in 2020 [1][3]. Increase in incidence, altogether with predictive models for future years, prove that CRC is a growing burden for patients and national healthcare systems [4]. A significant shift toward the growing incidence among younger adults (<50 y.o.) makes those predictions even more worrisome [5]. The COVID-19 pandemic led to weighty health care delivery disruptions also in the matter of the prevention and treatment of patients with CRC [6][7]. The association between the risk of a more advanced stage of disease and the COVID-19 pandemic was reported in patients undergoing CRC when compared with pre-pandemic cases [8]. Limited access to health care and a CRC screening slowdown emphasized the importance of research in new diagnostic tools. Colorectal cancer is a nonhomogeneous group in which over 90% of cases are adenocarcinomas [9]. Long-term survival and cure rates have not improved significantly in recent years, especially in more advanced stages of the disease [9][10][11]. Carcinogenesis involves an accumulation of irreversible genetic mutations and epigenetic alterations. Within the same tumor, there are genetically distinguished cell populations coexisting. Epigenetic alterations vary from “hard-wired” and stable during cell division to transient and changing with every few divisions [12]. Epigenetic alterations, leading to developmental genes’ reactivation, normally silent in somatic tissues, have been observed in CRC specimens [13]. Not every genetical mutation and epigenetic alternation lead to specific phenotype change. Phenotypic plasticity has been described, also in CRC cells, showing that there is an ability to alter transcriptome without underlying genetic or epigenetic heritable mutation [14]. All the above mentioned sum up into a complex intra-tumor heterogeneity and are closely connected in cancer evolution. Clonal selection and

evolution are at the base of treatment resistance [13]. Approximately 60% of all CRCs are sporadic–they develop without any known family history or any obvious genetic cancer syndrome (e.g., FAP or HNPCC) [15][16]. One-in-four CRCs has a hereditary component, as family and twin studies show. Yet, environmental factors play a role in carcinogenesis in those cases. Only 5% of CRC is attributed to well-characterized, high-penetrance syndromes [17].

The prognosis for patients with CRC is strongly determined by tumor invasiveness and the development of local or distant metastases. The presence of advanced locally or disseminated disease is a strong negative prognostic for a cure and long-term survival. Surgical treatment remains at the base of a curative approach [10]. Big differences in overall survival, even within same-stage groups, place the search for valuable prognostic factors in the spotlight of clinical research [18][19]. Among many others, cell surface molecules are being investigated for their clinical relevance (e.g., carcino-embryonic antigen). Cell adhesion molecules (CAMs) play a role in diagnostics and remain a field of interest in pathophysiology and the development of new treatment strategies in CRC [20][21][22][23]. With modern improvements researchers are on the verge of introducing a wide array of prognostic and predictive tools into clinical practice, which will help treatment decision making [24]. Advanced statistical tools can help with navigation through numerous biomarkers, combining individual and distinct features into more relevant groups–e.g., consensus molecular subtypes classification of CRC as a prognostic and predictive instrument for clinical decisions [25][26][27] Factors, once associated only with poor prognosis, lead researchers to new therapy development (e.g., BRAF, HER2) [28]. The new methods, such as circulating tumor DNA (ctDNA) allow more precise and sooner detection of the residual disease or relapse [29][30][31]. Nectins and nectin-like molecule seem to be worthy research candidates for future clinical implementation.

2. Nectins and Necls in Cancer

2.1. Nectin-1

Nectin-1 is known as CD111, PRR-1, PVRL-1, and expressed under normal conditions on cells of the gastrointestinal tract, liver, gallbladder, female reproductive organs, and skin [32][33]. It is probably best studied as an entry receptor for the human herpes virus 1 (HSV-1) infection. Nectin-1 has gained additional attention due to its interactions with CD96 (known also as Tactile) [34][35]. Abnormal expression of Nectin-1 can be observed in tumors of epithelial origin, such as cervical squamous cell carcinomas, cancer-associated fibroblasts of pancreatic ductal adenocarcinomas, CRCs and gastric cancers, or malignant transformations of keratinocytes. The observed expression varies from low to high, and the published data are not consistent in this matter [36]. CD96/Nectin-1 interactions have not yet been fully explored, although studies have shown that cells with Nectin-1 expression have been more susceptible to NK-mediated cell toxicity compared to those with no expression [34]. It can be speculated that, if soluble ligands circulating in serum can competitively inhibit NK-cell activation, they can also induce the internalization and degradation of activating receptors on cell surfaces. Colon cancer might be a promising target for NK cell-based adoptive immunotherapy, and there is a need to investigate the role of Nectin-1 in further studies [37]. HSV-1 is a well-studied virus and was used as the first rationally designed replication-competent onco-lytic virus (RCOV). Moreover, a soluble variable domain of Nectin-1 was successfully used in an experiment as an “adaptor” for increasing the efficacy of an HSV-1 infection in CHO cells with no Nectin-1 expression. Based on

these findings, cancerous cells, which display enhanced Nectin-1 availability, may serve as a receptor for HSV-1 viral oncolysis [38].

Nectin-1 tends to be a possible prognostic factor in the disease-free survival of patients with CRC. Research conducted by Tampakis et al. showed that Nectin-1 is strongly expressed in the cytoplasm of CRC cells in comparison to adjacent cells. Nectin-1 expression in colorectal cancer is associated with a significantly worse three-year progression-free survival, therefore, identifying a group of patients at high risk of an early recurrence of the disease [39]. These findings correlate with studies on pancreatic ductal adenocarcinoma patients. Yamada et al. reported that diffuse Nectin-1 expression in the cancer-associated fibroblasts of pancreatic ductal adenocarcinoma patients is associated with invasion, metastasis, and shorter survival [40]. It is important to note that colorectal endometriosis, which represents the most aggressive form of endometriosis, is characterized by both an increased expression of Nectin-1 and a decreased expression of Necl-2 [41].

2.2. Nectin-2

Nectin-2 (also known as CD112 and PVRL-2) is expressed in a vast number of adult tissues [33]. There is an overexpression of Nectin-2 in tumors of epithelial origin, such as squamous cell carcinomas and in adenocarcinomas (e.g., colorectal, esophageal, lung, pancreatic, and gallbladder cancer). Besides involvement in cell–cell adhesion, Nectin-2 interacts with immune cells by binding to different immune receptors, including CD226 (DNAM-1, DNAX accessory molecule-1), T-cell immunoreceptor Ig tyrosine (TIGIT)-based inhibition motif (ITIM) domain, and CD112R [42][43]. Coupling with receptors of CD8+ T-cells and NKs to modulate immune functioning by mediating immune-activating or inhibitory signaling in leukocytes. Necl-5 binds to the same immune receptors as Nectin-2, and it has been proven in MCA-induced tumors of Necl-5-deficient mice that Nectin-2 upregulation compensates Necl-5 absence in immune surveillance. In this study, Nagumo et al. pointed out that there is some sort of modulation of expression between Nectin-2, Necl-5, TIGIT, DNAM-1, and CD96 since they did not observe any difference in tumor growth in the Necl-5-deficient mice model compared to wild phenotypes [44]. Nectin-2 has been found to play an important role in the process of the NK cell-mediated killing of colon adenocarcinoma cells. A functional blockage of Nectin-2 with a specific antibody led to the significant inhibition of NK cell cytotoxicity to a colon cancer cell [37]. Platelet cloaking of circulating tumor cells and releasing transforming growth factor beta (TGFß) from platelets is an evasion method to hide from immune surveillance [45]. Cluxton et al. reported that cancer cells cloaked by platelets had a significantly reduced expression of Nectin-2 and Necl-5 on the tumor cell surface. Simultaneously, TGFß mediated the CD266 downregulation on NK cell surface. This suggests that the “immune decoy” mechanism is mediated by platelets. Platelet cloaking actively disrupts the CD226/CD96–Nectin-2/Necl-5 axis of circulating cancer cells recognition and plays a significant role in metastatic cascade [46].

An estimated 3–5% of patients with diagnosed CRC display HER2 amplification. In recent years, this has emerged as an actionable therapeutic target. There are treatments targeted at HER2 in clinical trials, e.g., with trastuzumab-deruxtecan ADC in metastatic CRC [47][48]. Nectin-2 has an affinity with the inhibitory immune receptor CD112R present in T-cells and NK cells [49]. Trastuzumab has limited action on cells with low HER2 expression. Antibody blockage of CD112R-enhanced NK cell cytokine production when NK cells were incubated with trastuzumab-

coated breast cancer cells [50]. Thus, Nectin-2 and its receptors can be utilized to improve the therapeutic level of trastuzumab and can possibly be used in cases with lower HER2 expression. The complex and not yet fully explored TIGIT-CD96-CD112R-CD-226 axis is a promising target for a next generation of immunotherapy in cancer [35][43].

PVRIG binds with high affinity to Nectin-2 and suppresses T-cell function. This may lead to the presence of exhausted T-cell phenotypes in the tumor microenvironment (TME) that is unable to perform effective cytotoxicity. Whelan et al. found that PVRIG-Nectin-2 axis blockage enhanced cytokine production and the cytotoxic function of T-cells [51]. Immune-checkpoint inhibitors targeting the PVRIG-Nectin-2 axis in Nectin-2 positive cancers may be evaluated as potential drugs.

What is more, Nectin-2 is the target of post-translational modifications. Ubiquitination not only decreases Nectin-2 surface expression by targeting the protein for degradation but also by promotes Nectin-2 intracellular retention. Upon the inhibition of the ubiquitin pathway, increased Nectin2 surface expression renders tumor cells more efficiently recognized and lysed by NK cells by mediating the CD226-dependent co-stimulation of both NK and CD8+ T cells [52].

2.3. Nectin-3

Nectin-3, also known as PVRL-3, PRR3, or CD113, plays a significant role in organ development (e.g., ocular, inner ear, and cerebral cortex development) and is widely expressed in healthy adult tissues (e.g., endocrine, gastrointestinal tissues, testis). Nectin-3 has the most versatile skill in terms of trans-interactions with other family members [36][53]. It is the only known Nectin that is expressed on the T-cell surface. Nectin-3 plays a significant role in T-lymphocytes extravasation. It trans-interacts with Nectin-2 on endothelial cells (localized near high endothelial venules) and facilitates the transendothelial migration of immune cells to secondary immune organs or surrounding tissues [54]. A similar mechanism may apply to malignant cells during disease dissemination [55]. Nectin-3 was identified as a mandatory C. difficile receptor for TcdB-mediated cytotoxicity as it is highly expressed in the colon. It may serve as a drug-target to prevent pseudomembranous colitis symptoms in C. difficile infections [56]. There are no specific studies on the clinical application of Nectin-3 expression in CRC. From the published data, researchers know that Nectin-3 expression is upregulated in lung adenocarcinomas, ovarian, and nasopharyngeal carcinomas. Minawa et al. presented a study in which the membranous expression of Nectin-3 (normally absent in healthy lung tissues) was found to be associated with a poor prognosis for lung adenocarcinoma patients. Surprisingly patients who showed the membranous expression of Nectin-3 together with e-cadherin co-location had a better overall survival rate than in the case of the separate localization of both molecules within a tumor cell. In cases where Nectin-3 was expressed on a cell membrane with no expression of e-cadherin, the overall outcome was the worst of all patient groups. Thus, the membranous Nectin-3 that does not have a physiological function (the recruitment of E-cadherin) may contribute to increased tumor malignancy [57]. Zhao et al. established Nectin-3 and NRXN3 (both are members of CAMs) as downstream target genes of the zinc finger protein 582 (ZNF582). The hypermetylation of ZNF582 in nasopharyngeal carcinoma (NPC) is associated with higher migration, invasion, and metastasis. The restoration of ZNF582 led to the downregulation of Nectin-3 expression and the upregulation of

NRXN3. Subsequent knock-out experiments and an in vivo model confirmed that Nectin-3 acts as an oncogene in NPC. This study also elucidated a new way of regulating Nectin-3 expression by ZNF582 [58]. Similarly, Xu et al. reported that Nectin-3 overexpression in ovarian cancer is associated with a worse overall survival rate. As an oncogene, Nectin-3 contributes to tumor progression in ovarian cancer. These results indicate that the expression of Nectin-3 upregulates the expression matrix metalloproteinases (MMPs 1 and 2) and leads to enhanced migration and invasion in OC cells by inducing ECM degradation in the area surrounding the tumor [59].

2.4. Nectin-4

This is probably the most extensively researched Nectin family member in cancer and disease in general, and in breast cancer in particular. Nectin-4, known also as PVRL-4 or PRR4, is strongly expressed in fetal tissues during development. There is little or no expression in adult tissues, besides the placenta, throat, bladder, breast, stomach, esophagus, salivary gland (ducts), and skin (epidermis and sweat glands) [36][60][61]. The importance of Nectin-4 during embryogenesis can be illustrated with the example of ectodermal dysplasia syndactyly associated with missense mutations of the PVLR4 gene. Disturbed trans-interactions between Nectin-1 and Nectin-4 causing Rac1 pathway alteration and delayed AJs formation in mutant cells are responsible for phenotypic presentations of EDSS1 and CLEPED1 [62][63][64]. By contrast, it was observed that Nectin-4 is overexpressed in various types of tumors (e.g., colorectal, gastric, esophageal, urotherial, breast, ovarian, hepatocellular, non-small cell lung carcinoma, and renal papillary cell) [61][65][66][67][68][69][70][71]. Its role as an oncogene is being investigated.

Nectin-4 has been identified as a biomarker of cancer stem cells (CSCs). CSCs have been recognized as the root of cancers' initiation and the resistance of cancer cells to conventional chemo- and radiotherapies; hence, they are critical in the metastasis, recurrence, and thus, the disease-free survival of, e.g., colorectal cancer [72][73][74]. Siddharth et al. alleged that Nectin-4 is a CSC biomarker in the breast cancer model. Nectin-4 deletion inhibited the invasion of EMT/TME, a WNT-signaling cascade and an anchorage-independent growth [75].

Colon cancer cells exposed to 5-fluorouracil (5-FU, a core drug in CRC chemotherapy worldwide) increased endogenous Nectin-4 expression. The 5-FU sensitivity is inversely related to Nectin-4 expression in CRC cell line studies. Thus, it has been proposed that Nectin-4 is one of the factors related to 5-FU resistance. Nectin-4 coupling with afadin and subsequent cell growth induction through the Pi3k/Akt axis is a putative mechanism of resistance to 5-FU therapy in CRC cells. A combination of BCNU and resveratrol-induced apoptosis in 5-FU resistant colon cancer cells by decreasing Nectin-4 expression [76].

2.5. Nectin-like Molecule 5

Nectin-like Molecule 5 (Necl-5), also known as polio-virus-receptor (PVR), Tage4, or CD155, is phylogenetically more closely related to Nectins than to other Nectin-like molecules. It has probably diverged from Nectin-2 [77]. It trans-interacts with Nectin-3 on neighboring cells and also mediates cell–ECM junctions by binding to vitronectin. Necl-5 takes part in the contact inhibition mechanism. When there is no cell–cell contact, Necl-5 prevents Sprouty2 (Spry2) phosphorylation. After cells come into contact with each other, Necl-5 is downregulated by endocytosis

following transient trans-interaction with Nectin-3. Unprotected Spry2 is tyrosine-phosphorylated by c-Src, which is activated by the PDGF receptor in response to PDGF, and subsequently inhibits PDGF-induced Ras signaling for cell proliferation [53][78]. Upregulation of Necl-5 in cancerous transformed cells that exceed the rate of internalization during cell–cell contact has been proven in studies to increase cell proliferation and hence tumor progression [79]. Necl-5 colocalizes with integrin on leading edges and takes part in growth factor-induced lamellipodia formation [78]. Necl-5 is upregulated through the Sonic hedgehog pathway as well as in Ras-mutated cells and allegedly induces cancer cells proliferation by inter alia shortening the G0/G1 phase [80].

Through interactions with CD226 and TIGIT, molecules present on leukocytes, Necl-5 together with Nectin-2 is a key regulator in cell-mediated immune response [35][81].

By binding to TIGIT, Necl-5 induces immunosuppression by the inhibition of NK cell and CD8+ T-cell cytotoxicity [82]. At the same time, Necl-5 has an affinity to the DNAM-1 molecule, which enhances immunological response by recognizing and killing tumors [83].

Necl-5 is known to be overexpressed on various types of malignant cells, including CRC [84][85]. Zheng et al. evaluated Necl-5 in CRC cell lines under different conditions. They observed increased apoptosis, inhibited colony formation ability, and cell cycle arrest in the G1 phase in CRC cells after Necl-5 knockdown. In addition, the authors observed reduced expression of some cell-invasion-related molecules, such as FAK, Src, and MMP-2. Necl-5 knockdown inhibited Akt phosphorylation. Taken together, their findings support previous studies on that subject—Necl-5 attributes to tumor progression, invasion, and metastases in CRC cell lines and may be considered an anti-apoptotic factor in CRC [84]. Morimoto et al. indicated that Necl-5 augments the metastasis of cancer cells, including CRC, to the lungs. Necl-5 mAb blockage reduced secondary tumor formation in lungs by 60% in a mice model [86]. The authors suggested that cancer cells with high Necl-5 expression attach to CD226-expressing platelets. The mentioned process leads to platelet cloaking and enhances immune evasion of cancerous cells. Cell aggregates were arrested in pulmonary capillaries where extravasation and metastases formation take place [46][86].

There are many examples of the importance of Necl-5 in carcinogenesis, CRC progression, and dissemination. Necl-5 is also involved in immune surveillance and can act both as a tumor inducer and suppressor. Therefore, research on the application of Necl-5 in diagnostics and treatment strategies is recommended.

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