


Review Article

CLEC12A: A Promise Target for Cancer Therapy

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Introduction

Cancer is the leading cause of mortality in every country in the world [1]. The World Health Organization reported that cancer is one of the major causes of disease-related deaths before the age of 70 [2]. Globally, cancer incidences and mortality is alarming and can often be co-related with the socio-economic development of a given population. This concern was depicted in 4-tier Human Development Index (HDI) of the United Nation [3]. An estimated 19.3 million fresh cases and 10 million deaths were registered globally in 2020. Of these, most new cases are of female breast cancer and maximum mortality rate is of lung cancer among both sexes. The cases of blood cancer are also distressing with 711,795 deaths among 1,278,362 new cases registered in 2020 [4]. Worldwide cancer statistics show disconcerting rates of occurrences and deaths even after recent advances in healthcare. Treatment of cancer continues to be a challenge since it is often difficult to appropriately categorise them, based on their underlying molecular signatures. Therefore, elucidating key signaling markers and their role in different types of cancers is a pre-requisite. Research on the haematological niche has progressed in the recent years [5]. The complexity of the human bone marrow, with context to haematological malignancies, is more difficult to elucidate with the present strategies compared to the niche of solid tumors. There can, however, be few similarities between the two, as the bone marrow is a common site of metastasis of solid tumors too [6]. Relevant information has now been established on solid tumors and their micro-environments, which include immune, endothelial and mesenchymal cells. Albeit a gap in knowledge still exists, the need to discover definite means to interfere with the complex interplay between the niches is imperative to define efficient chemotherapeutic strategies in future.

Role of PRRs in the Immune System

In accordance, attempts have been made to establish a link between the immune system and the tumor microenvironment, to comprehend tumor progression and achieve effective therapeutic approaches. The innate and adaptive immunities work in co-ordination as the defence mechanisms of the immune system. Their primary role is to protect from harmful pathogens and maintain a symbiotic relationship with beneficial organisms colonizing within our system [7]. In innate immunity, immune cells are activated by their pattern recognition receptors (PRRs), which bind to pattern molecules of invading pathogens. The most common and widely studied PRRs are toll-like receptors (TLRs) and C-type lectin receptors (CLRs) [8]. Their response involves antigen capture, enhancing their MHC-II presentation receptors and production of chemokines and/or cytokines at the site of inflammation [9]. The TLRs and CLRs of the immune cells work in coordination with the immune

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system. The TLR expression has been identified in different subsets of dendritic cells (DCs), T-cells, basophils, mast cells, macrophages, eosinophils, neutrophils and monocytes [10]. The N-terminal domain of TLRs is associated with ligand binding. The ligands include molecular patterns like lipopolysaccharides (LPS), which are the constituents of the outer membrane of gram negative bacteria. The most widely studied TLR associated with LPS ligand binding, interaction and downstream activation, is TLR-4. On the other hand, the C-terminal which is the cytoplasmic domain of TLRs has a homology with interleukin type-1 receptor (IL-1R), known as Toll IL-1R receptor (TIR) domain [11]. This domain interacts with adaptor molecules and activates a cascade which regulates the inflammatory status in cells [12]. The main two adaptor molecules which are recruited to the TIR domain are myeloid differentiation primary response gene 88 (Myd88) and TIR domain-containing adaptor-inducing interferon (IFN)- β [TRIF or Toll-like receptor adaptor molecule 1 (TICAM-1)]. The adaptors channelize a signaling cascade that can eventually activate the NF- κ B family of transcription factors, resulting in increased transcription of pro-inflammatory cytokines and augmentation of inflammatory response by the immune system [13]. CLRs are expressed in endothelial cells, DCs, monocytes, macrophages and Langerhans cells. The family of PRRs are slightly more complex compared to the TLRs. The major attribute for CLRs is that they have a carbohydrate-recognition domain (CRD) which can sense and bind to carbohydrate molecular patterns with Ca^{2+} ions, even though some CLRs can bind to carbohydrate independent of Ca^{2+} [14]. The cytosolic tails of CLRs can have either immunoreceptor tyrosine-based activation motif (ITAM) domains or immunoreceptor tyrosine-based inhibition motif (ITIM) domains or do not clearly express any of these domains [15]. The ones with an activating moiety recruit spleen tyrosine kinase (Syk), while others recruit Syk by ITAM-associated adaptor molecules, e.g., Fc receptor γ -chain (FcR γ) or death associated protein 1 (DAP1) to induce pro-inflammatory responses like synthesis of key mediators, activation of inflammasomes and production of chemokines/cytokines [16]. On the other hand, CLRs with an ITIM motif interact with their Src homology region 2 domain-containing phosphatase (SHP)-1 and SHP-2 that is mainly responsible for the inhibition of the cascade initiated by different PRRs with ITAM or the TLRs [17,18].

Role of PRRs in Cancer

TLRs and Cancer

The crucial role of TLRs in immunological responses and inflammation extends beyond immune cells to cancer cells, even of non-myeloid origins. This is very interesting because cancer cells can employ receptors on their surface to enable their sustenance [19]. Activated TLRs on cancer cells can enhance cancer progression, promote anti-apoptotic

activity and induce resistance from the host immune system [20]. There are many cancer cells which express different types of TLRs that enhance the NF- κ B signaling cascade to bring forth an anti-apoptotic response and enhanced cancer cell proliferation [19]. They instigate cancer cells to release cytokines and chemokines and recruit specific immune cells to modulate the immune response at the tumor microenvironment [21]. Phase II clinical studies have been established with LPS and treatment of colorectal and lung cancer patients [22]. LPS induced activation of TLR-4 promotes the progression of ovarian cancer by releasing the anti-apoptotic protein, X-linked inhibitor of apoptosis (XIAP), and phosphorylated Akt [23]. TLR5 and TLR9 expressions have been shown to be associated with low to high grade cervical intraepithelial neoplasia (CIN) and invasive cervical squamous cell carcinoma [24, 25]. Furthermore, TLRs 2, 3, 4 and 9 are expressed in lung cancer cell lines. In lung cancer, TLR-4 activated by LPS has been shown to restrict tumor necrosis factor-alpha (TNF- α) and TNF-related apoptosis inducing ligand (TRAIL)-mediated apoptosis [26]. Researchers have also shown TLR-4 to be linked to prostate and head and neck cancers, and is over expressed in MDA-MB-231 human breast cancer cells [27]. On the contrary, it has experimentally been shown that toxins from gram negative bacteria shows anti-tumor effects [28]. Since the outer membrane of gram negative bacteria constitutes LPS which can activate TLRs, a school of thought argued that TLR activation could also lead to tumor regression [29]. Thus, contrasting literature indicates that TLR has a dual role in cancer cells, and can either modify cancer progression and chemo resistance, or suppress cancer metastasis [30].

CLRs and Cancer

It has been speculated that cancer cells, even from non-hematological origins, can employ specific receptors to evade immune attack and maintain disease progression [19]. Although the role of CLRs on solid tumor cells has not yet been elucidated, they have widely been shown to modulate the tumor microenvironment by sensing specific tumor associated antigens [31]. These antigens could be membrane proteins or transformed carbohydrate patterns, like glycoproteins or glycolipids on the cell surface, which are collectively termed as tumor associated carbohydrate antigens (TACAs) [32]. The CLRs can sense these molecular patterns; hence, these antigens are identified by the CLRs of the immune cells to initiate an immunological response. Certain CLRs, like dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), recognise carcinoembryonic antigen (CEA), a well-known tumor associated antigen, overexpressed in human colorectal gastric and pancreatic carcinomas [33]. Macrophage galactose C-type lectin (MGL) has a role in sensing and binding to Neu-5Ac-Tn and Neu-5Gc-Tn tumor associated antigens [34]. Dectin-1, another well-known CLR which

binds to β -glucans, has now been shown to recognise N-glycan structures on tumor cells. This was confirmed by N-glycosidase treatment, which impeded the anti-tumoral activity because of obliteration of these tumor antigens [35,36]. Plasmacytoid dendritic cells (pDCs) are involved in the production of type-I interferons (IFN- α and β), type III interferons (IFN- γ /IL-28/29) and other pro-inflammatory cytokines [37]. An efficient strategy for the elimination of tumors requires the participation of natural killer cells (NK cells), and tumor-specific CD8⁺ and CD4⁺ cells. The probable role of CLRs in alleviating this phenomenon has now been well established (38). MGL can sense Tn antigens and it is important for efficient internalization and presentation to CD4⁺ T cells [39]. Furthermore, commitment of MGL with these tumor-associated antigens over expresses maturation markers of DCs, enhances motility and most importantly intensifies CD8⁺ T-cell activation [40]. Remarkably, CLRs can mediate anti-tumor immunity by increased production of type I and III interferons. On the other side of the coin, CLRs can potentiate anti-inflammatory responses [41] and impede TLR-mediated protective immunity, eventually sustaining the tumor microenvironment by allowing tumor cells to escape immune response [42]. There also reports on the association of DC-SIGN with tumor-associated antigens [33]. Evidences shows that such associations sustain an anti-inflammatory response and restricts tumor associated macrophage (TAM)-associated inflammation of breast and adenocarcinoma patients. This response limits anti-tumor T-cell responses [43]. Since the specific role of CLRs and their expression on solid cancer cells have not been explored in detail, preliminary indications on their expression on different types of cancers can be procured from the Human Protein Atlas [44]. The Cancer Genome Atlas (TCGA) RNA seq dataset for RNA expression overview shows enhanced RNA expression of C-type lectin 9A (CLEC9A) in testis cancer cells. CLEC9A functions as an endocytic receptor on a group of myeloid cells specialized for the uptake and processing of material from dead cells. Another CLR, Killer Cell Lectin-like Receptor (KLRF1), which is involved in the (NK)-mediated cytolysis of PHA-induced lymphoblasts and its mRNA expression, was observed in BJ hTERT⁺, HAP1, and U-937 cell lines [45]. Although the role of CLRs in regulating the tumor microenvironment of cancer cells remain mostly obscure, their function in cancer came to light when C-type lectin family12 member A (CLEC12A), an inhibitory CLR, was revealed to be a promising marker for leukemia cancer stem cells in acute myeloid leukemia (AML) patients [46]. Exclusively, in this review, we want to steer the focus on CLEC12A as a CLR which is present on cancer stem cells and a putative candidate for direct targeting as part of an effective chemotherapeutic strategy.

CLEC12A

CLEC12A (also known as myeloid inhibitory C-type

lectin-like receptor, MICL) is an ITIM-containing inhibitory CLR, which are expressed by granulocytes, monocytes, macrophages and DCs [47,48]. This membrane-bound receptor is a homodimer and has been considered to be a marker for AML blasts. This indicates that CLEC12A has an important role in carcinogenesis, apart from its usual inhibitory functions in immune cells [47]. Supporting evidences have demonstrated that CLEC12A has endogenous ligands in cells, as soluble CLEC12A binds to single-cell suspensions isolated from different murine tissues [49]. It was primarily acknowledged that CLEC12A was an inhibitory CLR and marker for dead cells. Researchers have shown that human and murine CLEC12A identifies dead cells derived from 293T cells or thymocytes by employing a novel CLEC12A-immunoglobulin (Ig) fusion protein and reporter cells expressing CLEC12A-CD3 ζ chimera [50]. To further categorise the ligand for CLEC12A, investigators treated attenuated kidney cells with DNase, RNase, trypsin, and with an inhibitor of uric acid synthesis. Interestingly, only the uric acid inhibitor could eliminate CLEC12A-Ig binding to dead cells [51]. Uric acid is soluble in normal living cells, but upon cell death, it comes in contact with extracellular sodium ions, during which uric acid forms monosodium urate (MSU) crystals. MSU, which is released from dead cells, forms a damage-associated molecular pattern (DAMP). Since PRRs can sense signatures from dead cells, MSU acts as a direct ligand for CLEC12A [52]. Common inflammatory arthritis called gout occurs due to deposition of MSU crystals. In CLEC12A-deficient mice, neutrophil activation was studied in response to MSU. In this study, researchers have reported that MSU induces reactive oxygen species (ROS) generation in a Syk-dependent cascade, and this phenomenon was significantly heightened when CLEC12A was absent. Therefore, CLEC12A reduces MSU-responsive ROS production through inhibition of Syk activity [53]. Infiltration of neutrophils was elucidated in non-infectious inflammation, which was induced by dead cells *in vivo*. It was observed that response to dead cells was greatly increased in the absence of CLEC12A [54]. Therefore, CLEC12A as an inhibitory CLR, can sense dead cells and check sterile inflammation [55]. Expression of CLEC12A is reduced in pro-inflammatory conditions as it has a cytosolic ITIM domain, which can employ tyrosine phosphatases SHP-1 and SHP-2 to restrict the activation signals generated from the activating ITAM CLRs or the TLRs that induce inflammation [56]. CLEC12A was originally identified as an inhibitory CLR of the Dectin cluster of genes and can sense DAMPs like MSU. In contrast, another study showed that CLEC12A was activated upon sensing MSU which was released by dead cells from the host, but it also activated type-I IFN, thereby enhancing anti-viral immune response [57]. Hence, CLEC12A can maintain a balance between infection-induced inflammation and control of pathogens. In addition, inhibition of CLEC12A can clinically ameliorate persistent viral infection. CLEC12A is

thus expected to act by diminishing immune response, but research suggests that ITIM can stimulate, rather than hinder, immune response [47]. The question arises whether these receptors send information independently or with association with a co-receptor will require deeper investigation. However, the dual nature of CLEC12A has limited our understanding on this area and warrants more research.

CLEC12A as a Marker for Cancer Stem Cells

The preponderance of expression of CLRs on solid cancer cells and cancer stem cells has not yet been elucidated in detail. However, it has been revealed to be a promising marker for leukemia blasts in AML [58]. It has been shown that CD34⁺/CD38⁻/CLEC12A⁺ subsets were malignant and have functional stem cell-like properties in patients with AML [46]. This was specifically remarkable since normal hematopoietic stem and progenitor (CD34⁺/CD38⁻ and CD34⁺/CD33⁻ cell subsets) cells lack CLEC12A expression. Since then, researchers have considered therapeutic targeting of CLEC12A in treatment of AML. Erythrocytes, natural killer (NK) cells, B-cells and T-cells do not express CLEC12A; however, its expression was linked to common myeloid progenitors (CMP), granulocyte myeloid progenitors (GMP) and megakaryocyte-erythroid progenitor (MEP). Cells which are positive for CLEC12A in the hematopoietic lineage are classically defined CMPs [59]. Therefore, CLEC12A can serve both as a detection marker and could be translated to targeted therapy [60]. In AML patients, there are subsets of stem cells or progenitor cells which are either normal or malignant. Several biomarkers have been investigated to differentiate the subsets of cells, one such being CLEC12A. Healthy bone marrow CD34⁺/CD38⁻ subsets can be distinguished from CD34⁺/CD38⁻ subsets of AML patients, in which the later revealed CLEC12A expression [61]. To confirm that these CD34⁺/CD38⁻/CLEC12A⁺ subsets were cancer stem cells and have malignant properties, they were injected in immunodeficient mice. The results indicated leukemia-related phenotype and the cells remained CLEC12A positive [62]. CLEC12A expression was stable in chemo-treated and G-CSF-treated patients [63]. The CD34⁺/CD38⁻ cells were however negative for CLEC12A, confirming that chemotherapy did not up regulate CLEC12A expression. This study has shown that samples from patients obtained during diagnosis and relapse did not show significant alterations in CLEC12A expression [62]. On the contrary, another study indicated 45% CLEC12A expression during initial diagnosis and approximately 20% during relapse [64]. Hence, it is yet to be ascertained that CLEC12A expression is stable after chemo-treatment, although there may be other underlying factors that link CLEC12A expression on the cancer stem cells that can associate it with cancer relapse. To address this conundrum, scientists have now evaluated the link between measurable residual disease (MRD) and the expression of CLEC12A [65]. MRD was detected by multiparameter

flow cytometer with tagged antibodies which can detect the expression of antigens throughout treatment and relapse for differentially-expressed antigens, including CLEC12A [66]. Since CLEC12A is associated with leukemic blasts and leukemic stem cells (LSCs), therapies need to be developed targeting this appropriate diagnostic marker in the treatment of AML. CLEC12A targeted therapy will therefore most likely eliminate the residual cancer stem cells, leaving aside the normal stem cells, and will be a major breakthrough in management of AML.

Targeting of CLEC12A in AML

Monoclonal Antibodies

The use of monoclonal antibodies (mAbs) in treatment of AML, with emphasis on CD33 and CD123, has led to FDA and EMA-approval of the CD33 antibody with a drug conjugate gemtuzumab ozogamicin (Mylotarg). This mAb along with the drug conjugate mediates a dose-dependent complement-based cytotoxicity (DDCC) and an antibody dependant cell cytotoxicity (ADCC). The mAbs were efficiently internalized in HL-60 cells upon binding with CLEC12A. Both CD33 and CLEC12A were found to be highly upregulated at the RNA level and displayed increased cell surface expression on AML cells, as detected by flow cytometry, and are preferential immunotargets in management of AML [67]. Moreover, a lead chimeric CLEC12A mAb reduced the tumor mass in a xenograft model implanted with HL-60 cells. Several *in vitro*, *ex vivo* and *in vivo* experiments have revealed that CLEC12A mAbs have effective cytotoxic potential against CLEC12A-bearing cells. Although the results have been validated, phase I trials still need to confirm their therapeutic efficacy [68].

Antibody-Drug Conjugates

To further increase effectiveness of AML therapy, an anti-CD33-calicheamicin antibody-drug conjugates (ADC) has been developed [69]. However, treatment with this drug conjugate has led to side-effects, like thrombocytopenia. To overcome this drawback, an anti-CLEC12A ADC was developed, that employs a pyrrolobenzodiazepine dimer DNA alkylating and cross-linking agent [70,71]. This was developed by conjugating a novel self-immolative disulfide linker. This ADC proved to be effective against CLEC12A⁺ blasts of AML patients and tumor cells in AML xenograft models. Furthermore, in cynomolgus monkeys, no target independent toxicities were observed when administering the doses [71]. Another recent ADC that was developed was CLT030, construction of which was based on a humanized anti-CLEC12A antibody with two engineered cysteine residues, which are linked covalently by a cleavable linker to the DNA-binding D211 payload, isoquinolidinobenzodiazepine [72]. Upon binding to CLEC12A-expressing cells, it releases its DNA binding payload, is internalized and the linker is cleaved in the lysosome. It has shown strong efficacy in AML

in vitro and in the AML patient-derived *in vivo* model. When compared to CD33-ADC, differentiation of healthy human CD34⁺ cells into various lineages was less affected. This study further proved its potential in treatment of AML and results from clinical studies are awaited [73].

Bispecific Antibodies

While mAbs proved their worth in AML treatment, they have completely exploited the potential of the immune system to eliminate underlying malignancies. To further develop the efficacy of antibody therapy, bispecific constructs have been created, not only to recognize the epitope on the cancer cell, but also to activate the immune responsive cells (CD3 on T-cells or CD16 on NK-cells; [74,75]. Originally, bispecific mAbs were developed by chemical cross linking or by exchange of different heavy chains as a result of fusion of two hybridoma cell lines, but their efficacy was restricted by human anti-rat and anti-mouse antibodies, the need for high effector-to-target (E:T) ratios and low yields [75,76]. Over the course of time, other bispecific antibody constructs has been developed, which lead to improved therapeutic outcome, as confirmed by trials performed in B-cell acute lymphatic leukemia (B-ALL), using the CD19/CD3 BiTe (Bispecific T-cell engager), blinatumomab [77]. MCLA-117, a novel T cell-redirecting antibody for AML treatment was engineered, targeting CD3 on T cells and CLEC12A on leukemic cells. MCLA-117 can effectively instruct T cells to kill tumor cells while sparing the healthy hematopoietic compartment of the bone marrow. This bispecific antibody is a full length human IgG1 antibody that uses a common light chain, an anti-CLEC12A specific heavy variable gene segment and a CD3 VH heavy variable gene segment. The Fc portion of this antibody was constructed to allow heavy chain hetero-dimerization. Clinical trial of this promising bispecific antibody is presently ongoing [78,79].

Chimeric Antigen Receptor (CAR)

Over the last few years, genetically-engineered immune effector cells expressing chimeric antigen receptors (CARs) have been developed. Primary targeting CD19 have revealed strong anti-tumor potential in patients with B-lymphoblastic leukemia and other B-cell lymphoid malignancies [80-82]. This accomplishment has led to an interest in using similar approaches for the treatment of AML. Early focus with CARs and hybrid single-chain receptors were engineered with an extracellular tumor antigen. CLEC12A CAR T-cells has also been constructed which can target CLEC12A⁺ hematopoietic progenitor cells but not CD34⁺/CD38⁻ cells from healthy donors. *In vitro* assays reveal that the CLEC12A-CD33 CAR had specific anti-tumor activity against CD33⁺ and CLEC12A⁺ cells *in vitro*, as well as primary leukemia samples from AML patients [83, 84]. Murine malignancies were developed using cell lines expressing CD33 or CLEC12A and also by using the AML cell line U937 cells. In these models, CAR-T cells

significantly reduced tumor size and reduced mortality [85]. CLEC12A is an ideal target for chimeric antigen receptor T-cell (CAR-T) therapy for AML and its expression is closely linked with treatment response and patients' survival outcome. CLEC12A plays an important immunomodulatory role in AML [86]. Bridging proteins have now been developed and are designated as 'CAR-T cell engagers' which is a CAR-targeted protein fused to antigen binding domains derived from antibodies. Therefore, a CD19-anti-CLEC12A bridging protein that can bind to CAR19-T cells and CLEC12A was developed. These CAR19-T cells secrete bridging proteins and have cytotoxic activity against aggressive leukemic cell lines [83].

Trispecific Killer Engager

To achieve effective targeting of leukemic blasts and leukemic stem cells, a trispecific killer engager (TriKETM) molecule containing a humanized anti-CD16 heavy chain camelid single-domain antibody (sdAb), that activates NK cells, was conceived [87]. An IL-15 molecule that drives NK-cell priming, expansion and survival, and a single-chain variable fragment (scFv) against human CLEC12A (CLEC12A TriKE) was developed, which induced NK-cell proliferation, activation and killing of both AML cell lines and primary patient-derived AML blasts *in vitro*, while sparing healthy hematopoietic stem cells (HSCs). NK cells are important players in cancer immunotherapy. They can target and eliminate cancer cells by releasing cytotoxic granules or by CD16-mediated ADCC. CLEC12A TriKE can specifically target CLEC12A⁺ cells and can mediate its annihilation by NK cells. This efficient therapeutic strategy is now under phase I/II trials [87].

Expression of CLEC12A on Cancer Cells of Non-Hematopoietic Origin

There is insufficient evidence regarding expression of CLEC12A on cancer cells of non-hematopoietic origin. The Human Protein Atlas database records that CLEC12A expression highly correlates with urothelial cancer. There are sufficient records from patient samples on the expression of CLEC12A, but so far, there is no research on the role of CLEC12A on urothelial cancer. Furthermore, immunohistochemistry results show strong cytoplasmic staining in embryonal carcinoma of testis, stomach and urothelial cancer. It has been recorded in this database that 1 in every 10 patients with urothelial cancer show medium to high CLEC12A expression, whereas 1 in every 12 stomach and testis cancer patients show medium to high CLEC12A expression [88]. In another study, it was shown that upon silencing CLEC12A with siRNA, LCIII expression reduced significantly in HeLa cells. This study showed that CLEC12A is related to autophagy as LCIII is an autophagic marker, and paves a way to study the mechanism of CLEC12A and its relation in cancers of non-hematopoietic origin. Here,

CLEC12A is designated to be important for anti-bacterial autophagy. This was a remarkable study because a genome wide association study was done for Crohn's disease, a chronic inflammatory condition of the gastrointestinal tract. Nearly 140 genetic risk loci were recognized in which CLEC12A has shown to be related with autophagy. The authors have shown that silencing CLEC12A led to significantly reduced LCIII turnover which reverted upon overexpression of CLEC12A [89]. Since, autophagy is an important cellular physiology related to cancer prognosis, this study will open a new avenue in elucidating the role CLEC12A on cancer cells.

Summary

Pattern recognition receptors, like the TLRs and CLRs found on myeloid cells, sense patterns from microorganisms to orchestrate an immune response. TLRs and activating CLRs initiate a signalling cascade upon detection to activate the NF- κ B family of transcription factors and augment production of inflammatory cytokines. On the other hand, CLRs with inhibitory moieties can suppress this pro-inflammatory response by restricting the activation signal. CLEC12A is one such inhibitory CLR which suppresses inflammation by dampening the activation of NF- κ B. TLRs are expressed on cancer cells of non-myeloid origins. They have varied responses, can classically activate pro-inflammatory responses that lead to cancer progression or else suppress their development. There is, however, no definitive report of expression of CLRs on cancer cells of non-myeloid origins, till now, but it was recently elucidated that CLEC12A expression is related to the CSCs in AML. The role of CLEC12A in CSCs is largely unknown, and its presence on solid tumors has not yet been substantiated. Speculations implying that like TLRs, CLRs can also be present on tumors of non-haematological origins, led to the reports indicating that, CLEC12A has low to high expression in urothelial cancers. The exact mechanism by which it functions, and whether it behaves similarly to their myeloid counterparts is not yet known. Therefore, in this review we revealed a whole new avenue in the field of cancer research, indicating CLEC12A as a putative therapeutic target. How cancer cells can employ different myeloid receptors which are usually not expressed in non-hematopoietic cells, and how they use them to evade immune response and achieve their sustenance is a path which will be traversed in the years to come.

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