CD38 and Regulation of the Immune Response Cells in Cancer

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Cancer is a leading cause of death worldwide. Understanding the functional mechanisms associated with metabolic reprogramming, which is a typical feature of cancer cells, is key to effective therapy. CD38, primarily a NAD+ glycohydrolase and ADPR cyclase, is a multifunctional transmembrane protein whose abnormal overexpression in a variety of tumor types is associated with cancer progression. It is linked to VEGFR2 mediated angiogenesis and immune suppression as it favors the recruitment of suppressive immune cells like Tregs and myeloid-derived suppressor cells, thus helping immune escape. CD38 is expressed in M1 macrophages and in neutrophil and T cell-mediated immune response and is associated with IFNγ-mediated suppressor activity of immune responses. Targeting CD38 with anti-CD38 monoclonal antibodies in hematological malignancies has shown excellent results. Bearing that in mind, targeting CD38 in other nonhematological cancer types, especially carcinomas, which are of epithelial origin with specific anti-CD38 antibodies alone or in combination with immunomodulatory drugs, is an interesting option that deserves profound consideration.

1. Introduction

Cancer immunotherapy has progressed enormously since the identification of immune checkpoints. The list of putative stimulatory and inhibitory checkpoints so far clearly established is extensive: ICOS/ICOS-L, GTR/GTR-L, CD27/CD70, CD40/CD40-L, DNAM-1/LAG-3, PD1-L1/2, Galectin-9/TIM-3, and many more [1]. The search for new immune checkpoint targets is now centered towards the adenosinergic pathway and its metabolite adenosine (ADO), that support immune suppression within the tumor microenvironment (TME) [2, 3] as it limits the functionality of T, Dendritic, and NK cells, as well as macrophages and neutrophils [4]. The accumulation of adenosine in the TME is partly dependent on two ectoenzymes entangled in canonical and noncanonical pathways [5]. One is the ectonucleoside triphosphate diphosphohydrolase (NTPDase, CD39) that converts ATP released by cell lysis or by exocytosis of ATP-containing vesicles via transport vesicles or via lysosomes into AMP, and the other is ecto-5-nucleotidase (Ecto5’N-Tase, CD73) that dephosphorylates AMP into adenosine [6]. The generation of adenosine by a noncanonical pathway begins with NAD in a reaction run by the multifunctional transmembrane protein CD38 [7].

CD38 has come into consideration as its involvement in adenosine-mediated immunosuppression within the tumor microenvironment has been established [8]. CD38 is a multifunctional ectoenzyme that functions as a nicotinamide adenine dinucleotide (NAD+) glycohydrolase and catalyzes the synthesis and degradation of cADPR affecting calcium signaling and release, thus decreasing extracellular NAD+, altering calcium cascade and deeply contributing to adenosine-mediated immune suppression (Figure 1), which alters the activity of T, NK, and dendritic cells and attracts migration of suppressor cells like MDSCs, Tregs, and Bregs [9–11]. The effect upon immune cells is mainly via modulation of FasL expression [12–14]. Alterations in CD38/FasL
regulated apoptosis have been reported in myeloma [15, 16]
and in NK cells of gastric cancer patients [17, 18]. We have
recently gathered evidence that suggests the over-
expression of some tight junction proteins in gastric cancer
cells affects CD38-related FasL expression and activity on
NK cells. Our aim was to emphasize the role of CD38 on the
immune suppression of some malignant neoplasms and to
emphasize its role as an interesting target for cancer im-
munotherapy [19].

1.1. CD38 Structure. CD38 is a 45 kDa type II transmembrane
glycoprotein with a single transmembrane segment near its
N-terminus. It shares a 20–30% sequence identity with Aplysia
ADP-ribosyl cyclase, BST-1, also termed CD157, and a GPI-
anchored protein found in Schistosoma mansoni. It is formed
by two identical monomers that favor a physiologically stable
structure with a pocket at the middle of the cleft, that is, the
enzyme active site. The crystal structure of the extramembrane
domain, which is fully active enzymatically and is crystallized as
head-to-tail dimers, has been well determined [20, 21]. It is
expressed in high densities on plasma cells, plasmablasts,
natural killer cells, plasmacytoid dendritic cells, and activated B
and T lymphocytes in healthy subjects and in hematological
tumors including multiple myeloma [22].

1.2. CD 38 Function. CD38 functions as a lymphocyte re-
ceptor and transducer of signals and an ectoenzyme that
generates cyclic adenosine diphosphate-ribose involved in
intracellular calcium mobilization (Figure 1). First thought
to be expressed only on thymocytes and activated T cells,
CD38 was later found to be widely expressed on B cells,
circulating monocytes, dendritic cells, granulocytes, plasma
cells, both resting and circulating NK cells, neutrophils,
and granulocytes. CD38 is also found on the surface of eryth-
rocytes and platelets, where it plays an essential role, to-
gether with platelet/endothelial cell adhesion molecule 1
(CD31), in the microenvironment retention of cancer cells
[22]. CD38 is also expressed in the cytoplasm and nucleus of
nonlymphoid cells such as normal prostatic epithelial cells,
pancreatic islet cells, smooth and striated muscle cells, renal
tubules, retinal ganglial cells, and cornea.

As a surface receptor, CD38 is necessary for the acti-
vation and proliferation of immune cells. Its IFNγ and TNFα
induce its expression in macrophages and dendritic cells [23].
It establishes a weak and dynamic interaction with the
nonsubstrate ligand CD31, in an interaction necessary for
leukocyte adhesion and migration. CD38 has a very small
cytoplasmic tail suggesting it is unable to initiate a signaling
cascade and so it associates with other signaling receptors
such as TCR/CD3 in T cells, BCR (CD19/CD21) in B cells,
and CD16/CD61 in NK cells. In addition, CD38 ligation with
a counter ligand induces the expression and secretion of IL-
1β, IL-6, IL-10, and IFNγ from monocytes and T cells.
NAADP, produced through the enzymatic activity of CD38
[24], regulates T cell activation, proliferation, and chemotaxis.

CD38 is found in recycling endosomes that contain
perforin and granzymes in the immunological synapse when
the TCR of cytotoxic T cells is engaged. CD38 is expressed on
membrane rafts where it promotes cell signaling via AKT
and ERK activation and it is exported out of the cells through
the exocytic pathway. CD38 association with the signaling
complex CD16/CD61 in the NK cell membrane has a critical
role in transducing activating signals. CD38+CD8+ T cells
suppress the proliferation of CD38+CD4+ T cells [25], thus
indicating its capacity to modulate T cell subsets with reg-
ulatory properties. CD38 signaling upon ligation induces IL-
1β, IL-6, and IL-10 secretion and enhanced IL-12 production
in synergy with IFNγ in dendritic cells [26, 27].

High CD38 expression in immune cells such as Tregs, B
regs, MDSCs, and CD16-CD56 + NK cells contribute to a
change in their immune function [28–30]. A typical example
of the latter is represented by the CD4+CD25highFOX3+ Treg
cells with high CD38 expression that define a sup-
pressive subset of Tregs in multiple myeloma and non-
Hodgkin lymphoma via cytokine dependent mechanisms.
However, CD31- Tregs depicted reduced immune sup-
pressive activity that indicates the importance of CD38/
CD31 interaction in Treg mediated immunosuppression
[31]. CD38high B reg cells produce IL-10, which inhibits T
naïve cell differentiation to Th1 and Th17 cells while sup-
porting the proliferation of T reg cells [32, 33]. The immuno-
suppressive role of myeloid-derived suppressor cells
(MDSCs) is strongly expanded in the cancer microenvi-
ronment [29], which is well documented. CD38 expression
is considered as a marker of MDSCs activity and
CD38highMDSCs have more prominent immune suppres-
seffects. At the same time, MDSCs promote neo-
vascularization and tumor invasion (Figure 2).

1.3. CD38 and the Tumor Microenvironment. Tumor mi-
croenvironment (TME), a coordinated network of immune,
nonimmune, and cancer cells with other noncellular com-
ponents, is vital for the development, progression, immune
suppression, and persistence of cancer [35] as biological
processes such as hypoxia, angiogenesis, autophagy, apo-
ptosis resistance, and metabolic reprogramming are trig-
gered. The enhanced concentration of adenosine in the TME
leads to an increase or decrease of adenylate cyclase or
intracellular cyclic adenosine monophosphate in immune
cells expressing adenosine receptors (T cells, NK cells,
dendritic cells, neutrophils, macrophages), thus interfering
with the activation of immune cells and favoring tumor
progression [36, 37]. The accumulation of adenosine within
the TME causes immune suppression; targeting CD38 en-
zymatic activity would largely influence tumor cells.
Moreover, targeting CD38 will result in an accumulation of
NAD+ that is by itself a danger signal.

TME is also characterized by the presence of hypoxia due
to poor blood supply and increased oxygen consumption.
NAD+ is produced by the salvage pathway in hypoxic TME,
which is further converted to adenosine by CD38-expressing
cells, thus further suppressing the immune response by
recruitment of MDSCs, Tregs, tumor associated macro-
phages (TAMs) [38, 39]. Besides ADO arbitrated immune
suppression, CD38 bestowed NAADP is also involved in
VEGF mediated angiogenesis through its involvement in Ca+ signaling. VEGF interacts with receptors VEGFR1 and VEGFR2. VEGF binding to VEGFR2 leads to the release of Ca++ in a process where CD38 contributes [40–43]. Therefore, cells overexpressing CD38 in the TME direct the generation of an immune suppressive environment that reduces effector T cell functions but also promotes angiogenesis provides immune escape and helps in cancer progression. For instance, in chronic lymphocytic leukemia CD38+ clones in the TME have a survival advantage over CD38- clones as they depict higher migration towards the chemokine CXCL12 resulting in enhanced homing to lymphoid tissue and improved survival with higher expression of VEGF and antiapoptotic protein Mcl1 [44]. Metabolic reprogramming of NAD+ regulation via inhibition of CD38 has been proposed as a strategy for improving the efficacy of immune-based therapies and appears to play a significant role in the regulation of metabolism and immunomodulation of the tumor microenvironment [28, 45–47].

1.4. CD38 in Multiple Myeloma. Multiple myeloma is a type of cancer where malignant plasma cells overexpressing CD38 accumulate in the bone marrow. Interestingly, within the bone marrow microenvironment, myeloma cells are protected to CD38 antibody-induced cellular cytotoxicity by upregulating the expression of antiapoptotic molecules such as survivin [48]. Additionally, CD38 increases the phosphorylation of PI3K, AKT, and mTORC and upregulates the PI3K/AKT/mTOR pathway, which is related to metabolic reprogramming and proliferation of cancer cells, while such effects were significantly reversed with mTOR inhibitor, rapamycin [49, 50]. Indeed, mTOR and RICTOR are overexpressed in MM endothelial cells while mTORC2 and its downstream effectors are linked with an angiogenicswitch to MM [51]. This suggests inhibition of the PI3K/AKT/mTOR pathway with a dual mTOR inhibitor along with anti-CD38 therapies will exhibit a synergistic effect in CD38-expressing MM cells [51].

In this environment, the use of anti-CD38 mAbs depletes CD38+ MDSCs, Tregs, and Bregs immune suppressive cells and enhances antitumor activity [52, 53], but as anti-CD38 mAbs downregulates CD38 expression in tumor cells, immune escape, and disease progression is favored [54]. Histone deacetylase (HDAC) inhibitors (Panobinostat, Ricolinostat) upregulate CD38 RNA levels and CD38 surface expression on multiple myeloma cells [55], thus disrupting latency of the malignant cells. Interestingly, an all-trans retinoic acid (ATRA) combined with anti-CD38 treatment...
was able to reduce complement inhibitor proteins CD55 and CD59 expression on anti-CD38 resistant cells and improved complement-mediated cytotoxicity [56]. Ricolinostat decreases phosphorylation of AKT and mTOR downstream molecules, upregulates the expression of the Th1 transcription factor T-Bet, and decreases the suppressive function of Treg cells [57]. A significant decrease in IL-10 and Foxp3 in Tregs and improved proliferation and function of CD4+CD25− T cells and CD8+ and NK cytotoxic cells has been observed when an anti-CD38 monoclonal antibody was combined with lenalidomide, an immunomodulator that increases Th1 cytokine production and stimulates clonal T cell proliferation and NK cell activity [58]. STAT3, an oncogenic protein, has been targeted with a novel formulation of nanoparticles packaged with STAT 3 inhibitor linked with anti-CD38 mAb that improved uptake by MM cell lines; these nanoparticles depicted a 4-fold reduction in tumor size compared with nanoparticles carrying STAT3 inhibitor only [59].

1.5. CD38 in Epithelial Cancers. In esophagus cancer, tumor-derived signals such as IL-6, IGFBP3, and CXCL16 trigger the expansion of monocytic MDSCs with increased CD38 expression. This CD38+ MDSC population is halted in the early stages of differentiation, which express elevated levels of iNOS and increased activation of NFκB, resulting to be more potent in suppressing T cells in the TME. In CD38+ cervical cancer cells, the PI3K/AKT pathway and its downstream target gene p53 expression are upregulated [49, 60]. In gastric cancer, a CD19 + CD24hiCD38hi B reg population that plays immunosuppressive roles by producing IL-10 and TGFβ has been identified; this cell population is inhibiting cytokine production by CD4+ T cells and promotes the conversion of CD4 + CD25− effector T cells to CD4+FoxP3+Treg cells, which collectively promote tumor growth [30].

High CD38 expression has been observed in hepatic carcinoma TME and in tumor infiltrating lymphocytes (TILs). However, CD38 + TILs provide antitumor responses through secretion of cytotoxic compounds and inflammatory cytokines [61, 62]. These CD38+ TILs secrete high levels of IFNγ and in combination with Sorafenib, a kinase inhibitor used for advanced cancer [63], patients’ survival improves notably [64]. There is a CD38+ M1 macrophage population in TME that produces high levels of IL-6 and TNFα with concomitant CD80 expression, prompts more inflammation and helps in tumor suppression [63]. CD38 also serves as a coreceptor in MHC-II mediated T cell activation [65]. Increased CD38 expression induces immunosuppressive effects via its adenosinergic activity and can also cause resistance to anti-PD1/PDL1 treatment in HCC patients [66]. These results reinforce, understanding variability in CD38 expression of TILs in TME may improve the effectiveness of anti-PD1 immunotherapy with a suitable anti-CD38 agent.

Studies performed with CRISPR/Cas9-based knockout of CD38 in A549 adenocarcinoma human alveolar basal epithelial cell line exhibited inhibition of anchorage-independent cell growth, cell invasion, and xenograft growth in nude mice. This is consistent with results obtained with lung cancer cell lines and patient specimens that show increased levels of CD38 mRNA and protein expression of CD38 [67]. Blocking CD38 led to a significant decrease in Tregs within TME of an in vivo mouse model of lung cancer. CD38 is also involved in the control of nonsmall cell lung cancers (NSCLS), which cover 85% of lung cancers [68]. NSCLS treatment was centered on platinum-based chemotherapy followed by cytotoxic chemotherapy, but recently agents targeting CTLA-4 and PD-1 pathways have been included. Unfortunately, this treatment frequently develops resistance mediated by Interferon β and all-trans retinoic acid after a mean 5-week period, but Interestingly CD38+ CD8 T cells proliferation was induced after Interferon β and all-trans retinoic acid after a mean 5-week period, but Interestingly CD38+ CD8 T cells proliferation was induced after anti-PDL-1 therapy [69]. This CD38+ T cell population corresponds to early activated and nonexhausted effector cells [70]. The strong correlation between CD38 and inflammation in the TME supports the idea of combining anti-CD38 therapy with existing anti-PD-1/PDL-1 treatments.

Gliomas, frequent malignant brain tumors, respond poorly to conventional and recently developed cytotoxic chemotherapy. Nevertheless studies performed in CD38 deficient mice showed attenuated tumor size, progression, and improved life expectancy [71]. The glioma TME plays an important role in tumor progression [72]. Tumor associated microglia/macrophages (TMM), formed by a small proportion of resident brain CD38+ microglia and infiltrating monocytes, constitute 40% of the tumor [73, 74]. These TMMs secrete IL-1, basic fibroblast growth factor, VEGF, and regulate Ca++ mobilization via CD38 mediated cADPR, contribute to TMM activation, angiogenesis [75, 76], and immunosuppression, thus helping in tumor progression [77, 78].

In melanoma anti-PD-1 and anti-CTLA-4 based immunotherapies improve survival significantly in advanced cases [79, 80] while targeting CD38 in melanoma TME could provide synergistic effects. In mouse models, inhibition of CD38 restricted primary tumor growth and was associated with lower rates of pulmonary and brain metastasis as a result of promoted cell death, reduction in cancer-associated fibroblast, and prevention of angiogenesis. Targeting CD38 mediated NAADP synthesis, which is responsible for neo-angiogenesis and Ca++ signaling, with Ned-19, an NAADP inhibitor, constrained melanoma growth, vascularization, and metastasis [42]. Thus, reinforcing the importance of CD38 mediated NAADP inhibition in the activity of tumor-promoting components of the TME. An effect of CD38 inhibition is the reduction of adenosine in the melanoma TME that results in the inhibition of antitumor responses. Fortunately the addition of adenosine in primary melanoma cell lines restores the proliferation of CD4+ and CD8+ T cells [38, 81].

1.6. Anti-CD38 Agents and Their Therapeutic Use. Daratumumab is a human specific IgG1 anti-CD38 approved as a single agent or in combination regimens for the treatment of relapsed/refractory multiple myeloma [82, 83].
It triggers ADCC, CDC, and TAM in CD38+ multiple myeloma cells in both sensitive and drug resistance patients, modulates the enzymatic activity of CD38, and reduces adenosine levels [84, 85]. Daratumumab combined with dexamethasone and a proteasome inhibitor (Velcade) or a TNFα inhibitor (Revlimid) has been approved in patients with at least one previous line of therapy. A study on newly diagnosed transplant ineligible patients compared with the gold-standard bortezomib-Melphalan-Prednisone regimen with or without Daratumumab and found that the latter increased significantly the overall response rate and improved complete response and progression-free survival [86]. A similar improvement has been determined in newly diagnosed multiple myeloma and transplant-eligible patients treated with Daratumumab and the standard Velcade-Thalidomide-Dexamethasone regime [87]. Clinical trials with Daratumumab alone or in combination with hematological and nonhematological malignancies are in progress (Table 1) (Figure 3).

Daratumumab reduces suppressive cell types in the multiple myeloma tumor microenvironment [52] as it reduces CD38 expression, but as treatment progresses, it also increases the resistance to treatment. Though this reduction is transient, it is regained in 3 to 6 months after the drug infusion. Another important concern is the reduction of CD38+ NK cells even after the first infusion. Although CD38 expression is low, NK cells retain their activity and proliferate normally [88, 89]. In such a case, reinfusion of ex vivo expanded autologous NK cells can be used.
| Tumor type                                      | Drug                        | Patients | Title                                                                                                                                                                                                 | Reference          |
|-----------------------------------------------|-----------------------------|----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Carcinoma, non-small-cell lung                | Daratumumab + Atezolizumab  | 100      | A study of Daratumumab in combination with atezolizumab compared with atezolizumab alone in participants with previously treated advanced or metastatic nonsmall cell lung cancer                                                                 | NCT03023423        |
| Plasma cell myeloma                           | Daratumumab                 | 28       | Daratumumab in treating patients with multiple myeloma Study of Daratumumab in multiple myeloma (MM) patients in > VGPR/MRD-positive. Efficacy of Daratumumab in patients with relapsed/refractory myeloma with renal impairment A phase 2 study of nivolumab combined with Daratumumab with or without low-dose cyclophosphamide in relapsed/refractory multiple myeloma Phase 2 study to assess the clinical efficacy and safety of Daratumumab in patients with relapsed or refractory natural killer/t cell lymphoma, nasal type A phase 1 and phase 2 study of Daratumumab in combination with all-trans retinoic acid in relapsed/refractory multiple myeloma                                                                                                                                                                                | NCT02944565        |
| Multiple myeloma                              | Daratumumab + dexamethasone | 38       |                                                                                           | NCT03992170        |
| Multiple myeloma                              | Daratumumab + dexamethasone | 38       |                                                                                           | NCT03450057        |
| Relapsed/Refractory multiple myeloma          | Nivolumab-Dara/nivolumab-Dara With low dose of cyclophosphamide | 62       |                                                                                           |                    |
| Lymphoma                                      | Daratumumab                 | 32       |                                                                                           | NCT02927925        |
| Relapsed/Refractory multiple myeloma          | Daratumumab + ATRA          | 60       |                                                                                           | NCT02751255        |
| Pancreatic, non-small cell lung or triple negative breast cancers (advanced or metastatic solid tumors) | Nivolumab + Daratumumab | 120      |                                                                                           | NCT03098550        |
| Smoldering plasma cell myeloma                | Isatuximab                  | 62       |                                                                                           | NCT02960555        |
| Plasma cell myeloma                           | Isatuximab + cemiplimab     | 109      |                                                                                           | NCT03194867        |
| Multiple myeloma                              | Isatuximab + Bendamustine + prednisone | 37       |                                                                                           | NCT04083898        |
| Lymphoma                                      | Isatuximab + cemiplimab     | 130      |                                                                                           | NCT03769181        |
To overcome Daratumumab mediated resistance, the use of new drugs such as a synthetic derivative of all-trans retinoic acid, Tamibarotene (a.k.a Am80), that upregulates CD38 or anti-CD38 antibodies with different mechanisms of action such as Isatuximab, Felzartamab, or Mezagitamab is recommended [90]. Isatuximab is an IgG1 monoclonal antibody that induces apoptosis of tumor cells and ADCC; it binds to a specific

| Tumor type | Drug | Patients | Title | Reference |
|------------|------|----------|-------|-----------|
| Prostate cancer non-small cell lung cancer | Isatuximab + cemiplimab | 134 | A phase 1/2 open-label, multicenter, safety, preliminary efficacy and pharmacokinetic (PK) study of Isatuximab (SAR650984) in combination with REGN2810, or Isatuximab alone, in patients with advanced malignancies | NCT03367819 |
| Plasma cell myeloma | Isatuximab + lenalidomide + dexamethasone | 60 | A phase 1b study of SAR650984 (Anti-CD38 mAb) in combination with lenalidomide and dexamethasone for the treatment of relapsed or refractory multiple myeloma | NCT01749969 |
| Plasma cell myeloma | Isatuximab + lenalidomide + dexamethasone | 89 | A phase 1b study of SAR650984 (isatuximab) in combination with pomalidomide and dexamethasone for the treatment of relapsed/refractory multiple myeloma | NCT02283775 |

**Table 1: Continued.**

**Figure 3:** Dara mechanism of action. Dara exerts anticancer activity via Fc-dependent mechanism and immunomodulatory effects. Once bound to CD38 over cancer cells, Fc fragment of Dara allows engagement with Fc Receptors expressing effector cells, i.e., NK cells, T cells, neutrophils, and macrophages, leading to lysis (ADCC) or phagocytosis (ADCP) of the cancer cell. Engagement of Dara’s Fc with C1q outcomes activation of complement cascade and assembly of MAC complex over cancer cells and lysis (CDC). Dara’s binding mask CD38 ectoenzymatic activity reduces adenosine production and causes eliminations of immune suppressive cell types (i.e., Tregs, Bregs, MDSCs) that promotes T cell proliferation and effector functions (the figure is reproduced from the original figure published by Overdijk et al. [84] and distributed under the Creative Commons Attribution License).
discontinuous epitope containing amino acids located opposite to the catalytic site of CD38, thus almost completely inhibiting cyclase activity in a dose-dependent manner [91]. Continuous Isatuximab treatment did not cause a reduction in CD38 receptor expression in H929, MM1S, OPM2, and RPMI-8226 multiple myeloma cell lines. Furthermore, Isatuximab treated cells did not show the clustering of CD38 in polar aggregates that lead to the release of CD38 in microvesicles, an effect that conduces to Daratumumab resistance [92]. Isatuximab substantiated great antitumor activity alone or in combination with dexamethasone and immunomodulatory imide drugs that include lenalidomide, pomalidomide, and iberdomide [93].

Mesagitamab (TAK-079) is a cytolytic IgG1 anti-CD38 monoclonal antibody, which effectively removes CD38+ B cell lines by antibody-dependent or complement-dependent cytotoxicity [94].

Felzartamab (MOR202) is a Human Combinatorial Antibody Library derived human IgG1 anti-CD38 monoclonal antibody that, once attached, attracts natural killer cells, triggers ADCC and ADCP but not CDC, and shows synergistically enhanced cytotoxicity with Bortezomib and Lenalidomide.

Other anti-CD38 agents are currently being evaluated. CAR-T/TCR-T, Multi-CAR-T, TAK-573, TAK-169, T-007, AMG 424, and GBR 1342 are in phase 1/2 clinical development, while others like HexaBody-CD38, CD38-ARM (KP1196, KP1237), TSK011010/CID103, St1-S171, Anti-CD38/ IgF-1R bsAb scFV, Anti-CD38 SIFbod, CAR38-MILs, CD38 DART, and Actinium-225 are in preclinical developmental stages. The significant number of potential candidates under development points to the importance of CD38 in the control of several malignancies.

Because of what has been mentioned, the efficacy of anti-CD38 antibodies in many other cancers is being evaluated in preclinical and initial stages of clinical trials (Table 1).

2. Conclusion

CD38 has dual functions as an ectoenzyme and as a surface receptor that promotes migratory phenotypes and signaling cascades responsible for the activation and proliferation of various immune cells.

Both canonical and noncanonical pathways contribute to adenosine synthesis. However, is targeting CD38 alone sufficient to resolve ADO induced immunosuppression? CD38 expresses ubiquitously in immune populations like T cells, NK cells, and dendritic cells; therefore, targeting CD38 would reduce anti-inflammatory response and rejuvenate antitumor activity of immune cells. But the interconnecting links between CD38, CD39, and CD73 or with downstream adenosine receptors and the persistence of any compensatory mechanism available against CD38 depletion has to be further investigated. It is clear that the enzymatic and the surface receptor functions of CD38 are distinct from each other, and there is insufficient data available to justify which function of CD38 should be targeted for effective immune function restoration and hence, tumor elimination. Nevertheless, the development of anti-CD38 monoclonal antibodies has redefined the treatment landscape due to their ability to normalize immune cells function, thus triggering antibody-dependent cell-mediated cytotoxicity, complement-mediated cytotoxicity, antibody-dependent cellular phagocytosis of opsonized CD38+ cells, and direct apoptosis via Fcγ receptor-mediated crosslinking. As it has been clearly stated by Morandi et al.[93]; CD38 is a receptor with modulatory functions on immune regulatory cell subsets that warrants deeper analysis.

Conflicts of Interest

The authors declare that none of them has conflicts of interest.

Acknowledgments

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References

[1] C. Donini, L. D’Ambrosio, G. Grignani, M. Aglietta, and D. Sangiolo, “Next generation immune-checkpoints for cancer therapy,” Journal of Thoracic Disease, vol. 10, no. S13, pp. S1581–S1601, 2018.

[2] B. Zhang, “CD73 promotes tumor growth and metastasis,” Oncoimmunology, vol. 1, no. 1, pp. 67–70, 2012.

[3] P. A. Beavis, J. Stagg, P. K. Darcy, and M. J. Smyth, “CD73: a potent suppressor of antitumor immune responses,” Trends in Immunology, vol. 33, no. 5, pp. 231–237, 2012.

[4] S. Vigano, D. Alatouzi, G. Brinza et al., “CD73 targeting antitumour in cancer immunotherapy to enhance T-cell function,” Front Immunology, vol. 10, p. 925, 2019.

[5] F. Morandi, D. Marimpietri, A. L. Horenstein et al., “Microvesicles released from multiple myeloma cells are equipped with ectoenzymes belonging to canonical and non-canonical adenosinergic pathways and produce adenosine from ATP and NAD,” Oncoimmunology, vol. 7, no. 8, Article ID e1458809, 2018.

[6] S. Deaglio and S. C. Robson, “Ectonucleotidases as regulators of purinergic signaling in thrombosis, inflammation, and immunity,” Advances in Pharmacology, vol. 61, pp. 301–332, 2011.

[7] L. Horenstein, A. Chillemi, G. Zaccarello et al., “A CD38/CD203a/CD73 ectoenzymatic pathway independent of CD39 drives a novel adenosinergic loop in human T lymphocytes,” Oncoimmunology, vol. 2, no. 9, Article ID e26246, 2013.

[8] T. A. Karakashova, T. J. Waldron, E. Eruslanov et al., “CD38-Expressing myeloid-derived suppressor cells promote tumor growth in a murine model of esophageal cancer,” Cancer Research, vol. 75, no. 19, pp. 4074–4085, 2015.

[9] M. E. Moreno-García, L. N. López-Bojórquez, A. Zentella, L. A. Humphries, D. J. Rawlings, and L. Santos-Argumedo, “CD38 signaling regulates B lymphocyte activation via a phospholipase C (PLC)-y2-independent, protein kinase C, phosphatidylycholine-PLC, and phospholipase D-dependent
[40] B. Ben Baruch, E. Blacher, E. Mantsur et al., “Stromal CD38 regulates outgrowth of primary melanoma and generation of spontaneous metastasis,” *Oncotarget*, vol. 9, no. 61, pp. 31797–31811, 2018.

[41] A. Favia, M. Desideri, G. Gambara et al., “VEGF-induced neoangiogenesis is mediated by NAADP and two-pore channel-2-dependent Ca2+ signaling,” *Proceedings of the National Academy of Sciences*, vol. 111, no. 44, pp. E4706–E4715, 2014.

[42] A. Favia, I. Pafumi, M. Desideri et al., “NAADP-dependent Ca (2+) signaling controls melanoma progression, metastatic dissemination and neoangiogenesis,” *Scientific Reports*, vol. 6, p. 18925, 2016.

[43] A. S. Chung and N. Ferrara, “Developmental and pathological angiogenesis,” *Annual Review of Cell and Developmental Biology*, vol. 27, no. 1, pp. 563–584, 2011.

[44] C. Pepper, T. T. Lin, G. Pratt et al., “Mcl-1 expression has in vitro and in vivo significance in chronic lymphocytic leukemia and is associated with other poor prognostic markers,” *Blood*, vol. 112, no. 9, pp. 3807–3817, 2008.

[45] S. Chatterjee, A. Daenthanasanmak, P. Chakraborty et al., “CD38-NAD+Axis regulates immunotherapeutic anti-tumor T cell response,” *Cell Metabolism*, vol. 27, no. 1, pp. 85–100, 2018.

[46] K. A. Hogan, C. C. S. Chini, and E. N. Chini, “w’_he multifaceted ecto-enzyme CD38: roles in immunomodulation, cancer, aging, and metabolic diseases,” *Frontiers in Immunology*, vol. 10, p. 1187, 2019.

[47] M. R. Fernandez and J. L. Cleveland, “Metabolic reprogramming via targeting CD38 NADase augments adoptive T cell therapy,” *Cell Metabolism*, vol. 27, no. 1, pp. 3–5, 2018.

[48] N. W. C. J. van Donk and S. Z. Usmani, “CD38 antibodies in multiple myeloma: mechanisms of action and modes of resistance,” *Frontiers in Immunology*, vol. 9, p. 2134, 2018.

[49] S. Liao, S. Xiao, H. Chen et al., “CD38 enhances the proliferation and inhibits the apoptosis of cervical cancer cells by augmenting the mitochondria functions,” *Molecular Carcinogenesis*, vol. 56, no. 10, pp. 2245–2257, 2017.

[50] S. Liao, S. Xiao, H. Chen et al., “CD38 enhances the proliferation and inhibits the apoptosis of cervical cancer cells by augmenting the mitochondria functions,” *Molecular Carcinogenesis*, vol. 56, no. 10, pp. 2245–2257, 2017.

[51] A. Lamanuzzi, I. Saltarella, V. Desantis et al., “Inhibition of CD38-NAD+Axis regulates immunotherapeutic anti-tumor T cell response,” *Cell Metabolism*, vol. 27, no. 1, pp. 85–100, 2018.

[52] S. Liao, S. Xiao, H. Chen et al., “CD38 enhances the proliferation and inhibits the apoptosis of cervical cancer cells by augmenting the mitochondria functions,” *Molecular Carcinogenesis*, vol. 56, no. 10, pp. 2245–2257, 2017.

[53] J. Krejcik, T. Casneuf, I. S. Nijhof et al., “Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skew T-cell repertoire in multiple myeloma,” *Blood*, vol. 128, no. 3, pp. 384–394, 2016.

[54] L. Zhang, Y.-T. Tai, M. Ho et al., “Regulatory B cell-myeloma cell interaction confers immunosuppression and promotes their survival in the bone marrow milieu,” *Blood Cancer Journal*, vol. 7, no. 3, p. e547, 2017.

[55] I. S. Nijhof, T. Casneuf, J. van Velzen et al., “CD38 expression and complement inhibitors affect response and resistance to daratumumab therapy in myeloma,” *Blood*, vol. 128, no. 7, pp. 959–970, 2016.

[56] E. García-Guerrero, R. Götz, S. Doose et al., “Upregulation of CD38 expression on multiple myeloma cells by novel HDAC6 inhibitors is a class effect and augments the efficacy of daratumumab,” *Leukemia*, vol. 35, no. 1, pp. 201–214, 2021.

[57] E. García-Guerrero, T. Gogishvili, S. Danhof et al., “Ponobinostat induces CD38 upregulation and augments the antemyeloma efficacy of daratumumab,” *Blood*, vol. 129, no. 25, pp. 3386–3388, 2017.

[58] A. S. Laino, B. C. Betts, A. Veerapathran et al., “HDAC6 selective inhibition of melanoma patient T-cells augments antitumor characteristics,” *Journal for ImmunoTherapy of Cancer*, vol. 7, no. 1, p. 33, 2019.

[59] V. Kotla, S. Goel, S. Nischal et al., “Mechanism of action of lenalidomide in hematological malignancies,” *Journal of Hematology & Oncology*, vol. 2, no. 1, p. 36, 2009.

[60] Y. H. Huang, M. R. Vakili, O. Molavi et al., “Decoration of anti-CD38 on nanoparticles carrying a STAT3 inhibitor can improve the therapeutic efficacy against myeloma,” *Cancers (Basel)*, vol. 11, no. 2, 2019.

[61] S. Liao, S. Xiao, H. Chen et al., “CD38 enhances the proliferation and inhibits the apoptosis of cervical cancer cells by augmenting the mitochondria functions,” *Molecular Carcinogenesis*, vol. 56, no. 10, pp. 2245–2257, 2017.

[62] D. S. Chen and I. Mellman, “Elements of cancer immunity and the cancer-immune set point,” *Nature*, vol. 541, no. 7637, pp. 321–330, 2017.

[63] P. Bhat, G. Leggatt, N. Waterhouse, and I. H. Frazer, “Interferon-γ derived from cytotoxic lymphocytes directly enhances their motility and cytotoxicity,” *Cell Death and Disease*, vol. 8, no. 6, Article ID e2836, 2017.

[64] J. H. Lam, H. H. M. Ng, C. J. Lim et al., “Expression of CD38 on macrophages predicts improved prognosis in hepatocellular carcinoma,” *Frontiers in Immunology*, vol. 10, p. 2093, 2019.

[65] M. Garnele, A. Tan, Z. Her et al., “Interaction between tumour-infiltrating B cells and T cells controls the progression of hepatocellular carcinoma,” *Gut*, vol. 66, no. 2, pp. 342–351, 2017.

[66] M.-T. Zilber, S. Gregory, R. Mallone et al., “CD38 expressed on human monocytes: a coaccessory molecule in the superantigen-induced proliferation,” *Proceedings of the National Academy of Sciences*, vol. 97, no. 6, pp. 2840–2845, 2000.

[67] H. H. M. Ng, R. Y. Lee, S. Goh et al., “Immunohistochemical scoring of CD38 in the tumor microenvironment predicts responsiveness to anti-PD-1/PD-L1 immunotherapy in hepatocellular carcinoma,” *Journal for ImmunoTherapy of Cancer*, vol. 8, no. 2, 2020.

[68] X. Bu, J. Kato, J. A. Hong et al., “CD38 knockout suppresses tumorigenesis in mice and clonogenic growth of human lung cancer cells,” *Carcinogenesis*, vol. 39, no. 2, pp. 242–251, 2018.

[69] E. B. Garon, N. A. Rizvi, R. Hui et al., “Pembrolizumab for the treatment of non-small-cell lung cancer,” *New England Journal of Medicine*, vol. 372, no. 21, pp. 2018–2028, 2015.

[70] A. O. Kamphorst, R. N. Pillai, S. Yang et al., “Proliferation of PD-1+ CD8 T cells in peripheral blood after PD-1-targeted therapy in lung cancer patients,” *Proceedings of the National Academy of Sciences*, vol. 114, no. 19, pp. 4993–4998, 2017.

[71] T. Tassi, G. Grazia, C. Vegetti et al., “Early effector T lymphocytes coexpress multiple inhibitory receptors in primary non-small cell lung cancer,” *Cancer Research*, vol. 77, no. 4, pp. 851–861, 2017.

[72] E. Blacher, B. Ben Baruch, A. Levy et al., “Inhibition of glioma progression by a newly discovered CD38 inhibitor,” *International Journal of Cancer*, vol. 136, no. 6, pp. 1422–1433, 2015.

[73] A. Levy, E. Blacher, H. Vaknine, F. E. Lund, R. Stein, and L. Mayo, “CD38 deficiency in the tumor microenvironment attenuates glioma progression and modulates features of tumor-associated microglia/macrophages,” *Neuro-Oncology*, vol. 14, no. 8, pp. 1037–1049, 2012.

[74] M. L. Goodenberger and R. B. Jenkins, “Genetics of adult glioma,” *Cancer Genetics*, vol. 205, no. 12, pp. 613–621, 2012.
[74] F. B. Furnari, T. Fenton, R. M. Bachoo et al., “Malignant astrocytic glioma: genetics, biology, and paths to treatment,” *Genes & Development*, vol. 21, no. 21, pp. 2683–2710, 2007.

[75] B. Badie and J. Schartner, “Role of microglia in glioma biology,” *Microscopy Research and Technique*, vol. 54, no. 2, pp. 106–113, 2001.

[76] I. Yang, S. J. Han, G. Kaur, C. Crane, and A. T. Parsa, “The role of microglia in central nervous system immunity and glioma immunology,” *Journal of Clinical Neuroscience*, vol. 17, no. 1, pp. 6–10, 2010.

[77] A. Levy, A. Bercovich-Kinori, A. G. Alexandrovich et al., “CD38 facilitates recovery from traumatic brain injury,” *Journal of Neurotrauma*, vol. 26, no. 9, pp. 1521–1533, 2009.

[78] L. Mayo, J. Jacob-Hirsch, N. Amariglio et al., “Dual role of CD38 in microglial activation and activation-induced cell death,” *The Journal of Immunology*, vol. 181, no. 1, pp. 92–103, 2008.

[79] M. R. Albertini, “The age of enlightenment in melanoma immunotherapy,” *Journal for Immunotherapy of Cancer*, vol. 6, no. 1, p. 80, 2018.

[80] F. Spinella, V. Caprara, R. Cianfrocca et al., “The interplay between hypoxia, endothelial and melanoma cells regulates vascularization and cell motility through endothelin-1 and vascular endothelial growth factor,” *Carcinogenesis*, vol. 35, no. 4, pp. 840–848, 2014.

[81] F. Morandi, B. Morandi, A. L. Horenstein et al., "A non-canonical adenosinergic pathway led by CD38 in human melanoma cells induces suppression of T cell proliferation," *Oncotarget*, vol. 6, no. 28, pp. 25602–25618, 2015.

[82] M. H. Z. Guang, A. McCann, G. Bianchi et al., “Overcoming multiple myeloma drug resistance in the era of cancer “omics”,” *Leukemia & Lymphoma*, vol. 59, no. 3, pp. 542–561, 2018.

[83] S. Z. Usmani, B. M. Weiss, T. Plesner et al., "Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma," *Blood*, vol. 128, no. 1, pp. 37–44, 2016.

[84] F. Morandi, B. Morandi, A. L. Horenstein et al., "A non-canonical adenosinergic pathway led by CD38 in human melanoma cells induces suppression of T cell proliferation," *Oncotarget*, vol. 6, no. 28, pp. 25602–25618, 2015.

[85] M. B. Overdijk, S. Verploegen, M. B¨ogels et al., "Antibody-mediated phagocytosis contributes to the antitumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma," *Mabs*, vol. 7, no. 2, pp. 311–320, 2015.

[86] S. Z. Usmani, B. M. Weiss, T. Plesner et al., "Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma," *Blood*, vol. 128, no. 1, pp. 37–44, 2016.

[87] M. B. Overdijk, S. Verploegen, M. B¨ogels et al., "Antibody-mediated phagocytosis contributes to the antitumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma," *Mabs*, vol. 7, no. 2, pp. 311–320, 2015.

[88] I. S. Nijhof, R. W. J. Groen, H. M. Lokhorst et al., “Uptregulation of CD38 expression on multiple myeloma cells by all-trans retinoic acid improves the efficacy of daratumumab,” *Leukemia*, vol. 29, no. 10, pp. 2039–2049, 2015.

[89] M.-V. Mateos, M. A. Dimopoulos, M. Cavo et al., “Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma,” *New England Journal of Medicine*, vol. 378, no. 6, pp. 518–528, 2018.

[90] K. A. Frerichs, N. A. Nagy, P. L. Lindenbergh et al., “CD38-targeting antibodies in multiple myeloma: mechanisms of action and clinical experience,” *Expert Review of Clinical Immunology*, vol. 14, no. 3, pp. 197–206, 2018.

[91] J. Deckert, M. C. Wetzel, L. M. Bartle et al., “SA650984, A novel humanized CD38-targeting antibody, demonstrates potent antitumor activity in models of multiple myeloma and other CD38+ hematologic malignancies,” *Clinical Cancer Research*, vol. 20, no. 17, pp. 4574–4583, 2014.

[92] L. Moreno, C. Perez, A. Zabaleta et al., "The mechanism of action of the anti-CD38 monoclonal antibody Isatuximab in multiple myeloma," *Clinical Cancer Research*, vol. 25, no. 10, pp. 3176–3187, 2019.

[93] F. Morandi, I. Airoldi, D. Marimpietri, C. Bracci, A. C. Faini, and R. Gramignoli, "CD38, a receptor with multifunctional activities: from modulatory functions on regulatory cell subsets and extracellular vesicles, to a target for therapeutic strategies," *Cells*, vol. 8, no. 12, 2019.

[94] W. Korver, M. Carsillo, J. Yuan et al., "A reduction in B, T, and natural killer cells expressing CD38 by TAK-079 inhibits the induction and progression of collagen-induced arthritis in cynomolgus monkeys," *Journal of Pharmacology and Experimental Therapeutics*, vol. 370, no. 2, pp. 182–196, 2019.

[95] F. Morandi, I. Airoldi, D. Marimpietri, C. Bracci, A. C. Faini, and R. Gramignoli, "CD38, a receptor with multifunctional activities: from modulatory functions on regulatory cell subsets and extracellular vesicles, to a target for therapeutic strategies," *Cells*, vol. 8, no. 12, 2019.

[96] W. Korver, M. Carsillo, J. Yuan et al., "A reduction in B, T, and natural killer cells expressing CD38 by TAK-079 inhibits the induction and progression of collagen-induced arthritis in cynomolgus monkeys," *Journal of Pharmacology and Experimental Therapeutics*, vol. 370, no. 2, pp. 182–196, 2019.