



# CAM-DR: Mechanisms, Roles and Clinical Application in Tumors

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Despite the continuous improvement of various therapeutic techniques, the overall prognosis of tumors has been significantly improved, but malignant tumors in the middle and advanced stages still cannot be completely cured. It is now evident that cell adhesion-mediated resistance (CAM-DR) limits the success of cancer therapies and is a great obstacle to overcome in the clinic. The interactions between tumor cells and extracellular matrix (ECM) molecules or adjacent cells may play a significant role in initiating the intracellular signaling pathways that are associated with cell proliferation, survival upon binding to their ligands. Recent studies illustrate that these adhesion-related factors may contribute to the survival of cancer cells after chemotherapeutic therapy, advantageous to resistant cells to proliferate and develop multiple mechanisms of drug resistance. In this review, we focus on the molecular basis of these interactions and the main signal transduction pathways that are involved in the enhancement of the cancer cells' survival. Furthermore, therapies targeting interactions between cancer cells and their environment to enhance drug response or prevent the emergence of drug resistance will also be discussed.

**Keywords:** CAM-DR, tumor microenvironment, hematologic malignancies, signaling pathways, inhibitors

**Abbreviations:** EM-DR, environment-mediated drug resistance; SM-DR, soluble factor mediated-drug resistance; CAM-DR, cell adhesion mediated-drug resistance; NHL, non-Hodgkin's lymphoma; MM, multiple myeloma; VEGF, vascular growth factor; IL-3, IL-6, interleukin-3, 6; NO, nitric oxide; G-CSF, granulocyte colony-stimulating factor; BAFF, B cell-activating factor of the TNF family; GM-CSF, granulocyte-macrophage colony-stimulating factor; Bcl-2, B cell lymphoma-2; FN, fibronectin; VCAM-1, vascular cell adhesion molecule-1; VLA-4, integrin very late antigen-4; DDR, discoidin domain receptor; CXCR, C-X-C motif chemokine receptors; BMSCs, bone marrow stromal cells; MGUS, monoclonal gammopathy of unknown significance; SMM, smoldering multiple myeloma; HDACs, histone deacetylases; CAFs, cancer-associated fibroblasts; MDR, multi-drug resistance; BL, Burkitt's lymphoma; MCL, mantle cell lymphoma; ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; ABCC1, ATP-binding cassette C 1; PI3K, phosphatidylinositol 3-kinase; BTK, Bruton tyrosine kinase; CDC25A, M-phase inducer phosphatase 1; MRD, minimal residual diseases; HCC, hepatocellular carcinoma; CTGF, connective tissue growth factor; COL1A1, collagen 1A1; OSCC, oral squamous cell carcinoma; NPC, nasopharyngeal carcinoma; ECM, extracellular matrix; GC, gastric cancer; FAK, focal adhesion kinase; MAPK, mitogen-activated protein kinase; COL1, collagen type 1; NSCLC, non-small cell lung cancer; SCLC, small-cell lung cancer; GBM, glioblastoma multiforme; CRPC, castration-resistant prostate cancer; PFS, progression-free survival; OS, overall survival; JAK, Janus-activated kinase; STAT, signal transduction and activator of transcription; iNHL, inert non-Hodgkin's Lymphoma; ORR, overall remission rate; SLL, small lymphocytic lymphoma; FL, follicular lymphoma; BTZ, bortezomib; PDGFR- $\beta$ , platelet-derived growth factor receptor- $\beta$ .

## INTRODUCTION

Chemotherapy remains the major treatment of disseminated cancer including hematologic malignancies and metastatic solid tumors. Intrinsic and acquired resistance disseminated continues to be a considerable obstacle on our way to improve patient cures. Resistance mechanisms originate from pathological changes of intrinsic factors such as genetics, epigenetics, transcriptional regulation, and protein activation as well as extrinsic factors including the immune system, hypoxia, metabolism, and extracellular matrix (ECM). It was proposed that the tumor microenvironment, the non-cancerous cells, and ECM that are in direct contact with the cancer cell, may influence how cancer cells respond to chemotherapy. This influence mainly involves two aspects: a soluble factor and a contact factor. The first aspect involves soluble mediators, such as interleukins, that are secreted by non-tumor, stromal cells. It is capable of providing further signals for tumor cell growth and survival. The second aspect of tumor cell-environment interaction requires direct cell contact and has been given the term cell-adhesion-mediated drug resistance (CAM-DR). Recently, attention has been focused mainly on the effect of CAM-DR and cell adhesion to ECM proteins has been well clarified as a key and fundamental determinant of cancer therapy resistance. Adhesive interactions between cells or cells and ECM can influence cell behavior and tumor cell adhesion may influence cell survival and prevent drug-induced apoptosis. In this review, we will describe the current knowledge about cell adhesion resistance and put these findings into a clinical context and discuss the resulting consequences for the design of novel therapeutic strategies.

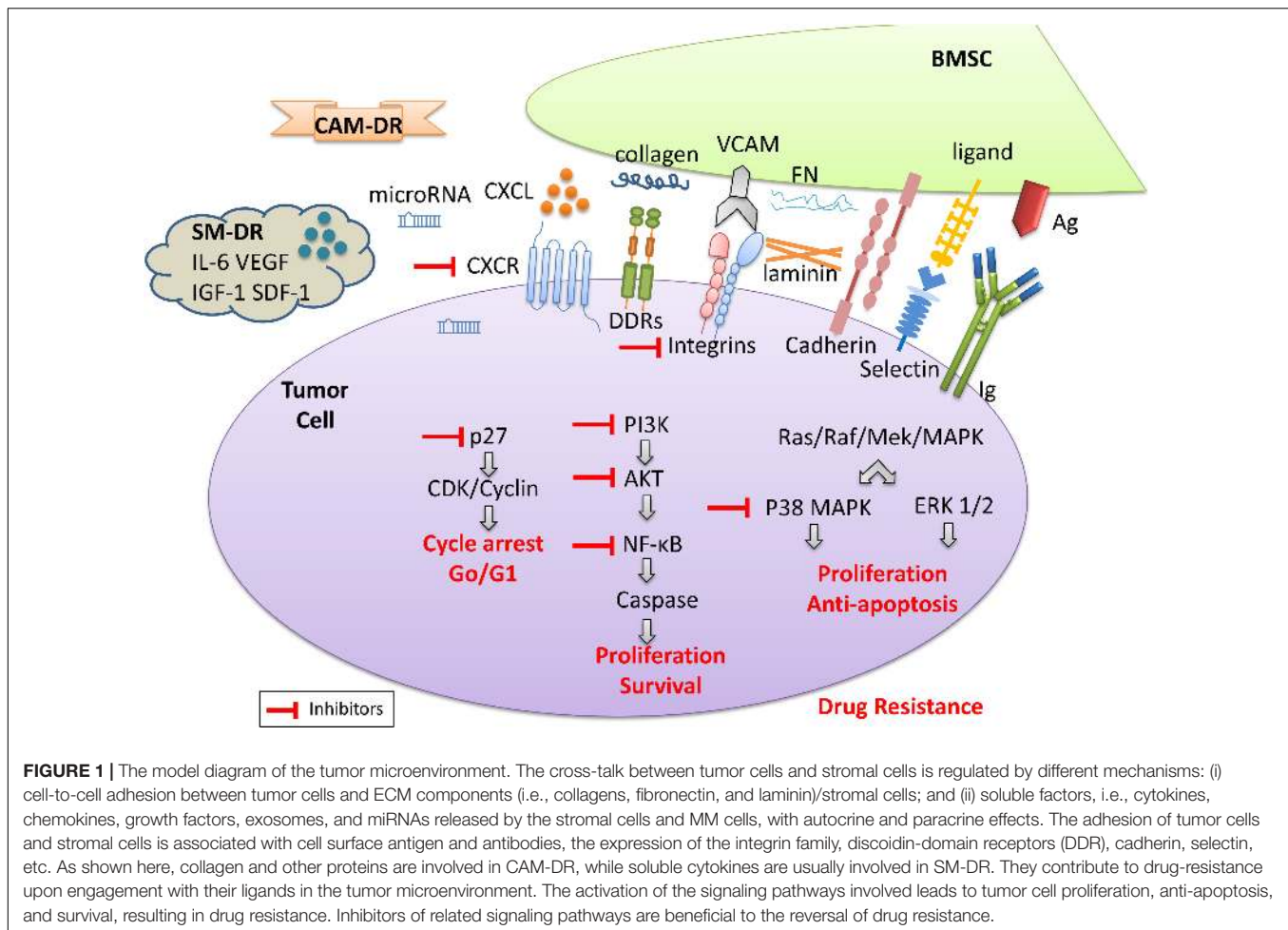
## MICROENVIRONMENT AND CAM-DR

The tumor microenvironment includes a non-cellular compartment formed by ECM proteins (i.e., laminin, fibronectin, and collagen) and soluble factors (i.e., cytokines, growth factors, chemokines, exosomes, and miRNAs), and a rich cellular compartment constituted by tumor cells and stromal cells (i.e., fibroblasts, osteoclasts, endothelial cells, and mesenchymal stromal cells) (Manier et al., 2012) (**Figure 1**). The tumor microenvironment provides support for the growth, proliferation, and invasion of tumor cells through intercellular connections and molecular interactions. Moreover, the tumor microenvironment plays an important role in drug resistance (Burger et al., 2009). Studies have found that hematologic malignant tumor cells die rapidly *in vitro*, which confirms the importance of the tumor microenvironment for tumor cell survival (Li and Dalton, 2006). A growing body of experimental data shows that hematological tumor cells can survive significantly longer when co-cultured with stromal cells *in vitro*. Within or surrounding the malignant tumor cells, stromal cells, lymphocytes, and endothelial cells are present which interact with each other and/or with the tumor cells. Besides, soluble factors in the tumor microenvironment provide signals for cell growth and survival. The cross-talk between tumor cells and stromal cells is regulated by different mechanisms: (i) cell-to-cell

adhesion between tumor cells and ECM components/stromal cells; and (ii) soluble factors, released by the stromal cells and MM cells, with autocrine and paracrine effects (Di Marzo et al., 2016). Thus, microenvironment mediated-drug resistance (EM-DR) in tumor cells can generally be divided into the intrinsic soluble factor mediated-drug resistance (SM-DR) and cell adhesion mediated-drug resistance (CAM-DR).

It has been reported that many soluble factors in the tumor microenvironment are related to the growth and survival of cells, such as vascular growth factor (VEGF) (Dias et al., 2002), interleukin-3, 6 (IL-3; IL-6) (Lee et al., 2004; Karakasheva et al., 2018), nitric oxide (NO) (Vedenko et al., 2020), granulocyte colony-stimulating factor (G-CSF) (Karagiannidis et al., 2021), B cell-activating factor of the TNF family (BAFF) (Lwin et al., 2009), etc. These soluble factors can not only stimulate the proliferation and survival of tumor cells but also lead to drug resistance. However, inhibition of these known soluble factor-mediated cell survival pathways does not overcome the phenomenon of drug resistance. Drug resistance mechanisms are multifaceted, such as gene mutations, cell cycle arrest, or CAM-DR through direct cell-to-cell contact and adhesion (Oshiro et al., 2001).

Compared with SM-DR in the tumor microenvironment, CAM-DR plays a greater role in the drug resistance of tumor cells. On the one hand, cell adhesion activates key signaling pathways leading to the expression of soluble factors and their receptors. For example, the interaction between hematologic tumor cells and stromal cells stimulates bone marrow stromal cells (BMSCs) to secrete IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF), while MM tumor cells secrete IL-6 and VEGF, etc. (Dalton, 2003). On the other hand, cell adhesion can lead to changes that cannot be caused by soluble factors. For example, reactivation of the expression of key molecules involved in drug resistance, such as the anti-apoptotic molecule c-FLIP<sub>L</sub>, leads to Fas-mediated apoptosis (Shain et al., 2002). Another example is topoisomerase II- $\beta$ , a key enzyme involved in the repair of DNA double-strand breaks, which can lead to drug resistance of tumor cells (Hazlehurst et al., 2001; Said et al., 2012). It also includes the increased expression of B cell lymphoma-2 (Bcl-2) and the activation of downstream signaling pathways (Yan et al., 2015), and so on, which represents a new mechanism of drug resistance. Cell adhesion is mediated by several families of adhesion molecules, including the immunoglobulin superfamily, integrins, cadherins, and selectins (Kim et al., 2020). The tumor microenvironment is abundant in binding partners for cell adhesion molecules as each component discussed above expresses diverse ligands and secret ECM (Malara et al., 2014; Galan-Diez et al., 2018; Zhao et al., 2019) (**Figure 1**). Fibronectin (FN), collagen, and laminin will interact with cell surface molecules (Zhang et al., 2019). Integrins are the most widely studied molecule at present (Elliott and Sethi, 2002). Integrin is a heterodimer receptor composed of two subunits  $\alpha$  and  $\beta$ . Up to now, 18  $\alpha$  subunits and 8  $\beta$  subunits have been identified (Miranti and Brugge, 2002). The expression of typical integrins is mainly  $\alpha 4\beta 1$  (integrin very late antigen-4, VLA-4) and  $\alpha 5\beta 1$  (VLA-5) in hematologic malignancies, especially VLA-4 is highly expressed in multiple myeloma (MM) cells and most normal B lymphocytes (Mraz et al., 2011). In myeloma cells, overexpression



of VLA-4 can subsequently lead to increased drug resistance, whereas the reversal a drug resistance is usually associated with decreased VLA-4 expression (Fontana et al., 2021; Sevilla-Movilla et al., 2020). Most integrins bind to ECM proteins (Hynes, 1992), among which the most important of which is fibronectin, which is the ligand of at least 10 integrin molecules. Cadherins can be classified into several different types including Type I and Type II classical cadherins (Ivanov et al., 2001). Stromal cells upregulate cadherin expression in leukemia cell lines and increase resistance to imatinib by stabilizing  $\beta$ -catenin (Chen et al., 2014). When interrupted the N-cadherin-mediated adhesion of chronic myeloid leukemia (CML) cells to BMSCs, the tumor cells gained sensitivity toward imatinib treatment (Zhang et al., 2013). Selectins (CD62) are single-chain transmembrane glycoproteins that mediate calcium-dependent carbohydrate-binding (Borsig, 2018). Hematological tumor cells interact with E-selectin through various ligands such as CD43, CD44, and PSGL-1 (Bistrrian et al., 2009). Although relatively specific ligands are preferentially bound in different cells, this does not mean that other ligands are less crucial in the CAM-DR of the disease. Interestingly, nilotinib treatment upregulated the expression of E-selectin, which may result in the increased adherence of leukemia cells to E-selectin and the evasion of the cytotoxicity induced by

chemotherapy (Hadzijušufovic et al., 2017). Discoidin domain receptors (DDR), including DDR1 and DDR2, are special types of the transmembrane receptor tyrosine kinase superfamily. DDR are activated by binding to the collagen and can activate signal transduction pathways. At the same time, DDR can regulate cell-collagen interactions which involved in multiple processes such as cell proliferation, migration, and apoptosis (Gao et al., 2021). Moreover, the IIGFs-DDR1 crosstalk is considered the major mediator of therapy resistance of cancer cells (Buck et al., 2010; Vella et al., 2019). The model diagram of tumor microenvironment is shown in **Figure 1**.

On this basis, the simplified model of the tumor microenvironment is to construct the FN model, that is, the interaction between tumor cells and FN leads to CAM-DR, which is convenient for the study of drug resistance caused by the adhesion of tumor cells to the ECM. At present, the models of CAM-DR have been widely used to simulate the interactions between tumor cells and tumor cells, tumor cells and ECM, and tumor cells and stromal cells. In addition to the FN model, there are also stromal models, which can be used to study CAM-DR and SM-DR. First proposed by the Dalton Laboratory, FN model allows the researchers to investigate the specific signaling pathways of CAM-DR which involved in cell adhesion associated

with FN or  $\beta 1$  integrin activation (Hazlehurst and Dalton, 2001), elucidating the role of two major adhesion molecules, VLA-4 and VLA-5, in hematological malignancies. One of the most typical findings of this model is that the activation of NF- $\kappa$ B signaling by FN is associated with the occurrence of CAM-DR (Landowski et al., 2003). Using the FN model, it was found for the first time that the down-regulation of the apoptotic protein Bim in myeloma was closely related to CAM-DR. This finding also proved that the integrin-mediated signaling pathway in myeloma is similar to the role of EGFR in the EGFR signaling pathway and can regulate the expression of Bim protein (Hazlehurst et al., 2003). FN adhesion model can also cause cell cycle arrest in the G1 phase, increase the expression of cell cycle inhibitor p27 (Lwin et al., 2007a), and inhibit the activity of CDK2 (Jiang et al., 2000b), a key molecule of cell division. Clinically related studies have found that G1 phase arrest of the cell cycle can significantly reduce the efficacy of drugs (Jiang et al., 2000a). These findings also explain the rapid proliferation of tumor cells in the microenvironment and their insensitivity to cytotoxic drug killing mechanisms. However, the FN model ignores the fact that stromal cells play a more complex role in the tumor microenvironment than fibronectin. The matrix model constructed by the cell compartment culture system can enable researchers to eliminate the interference of SM-DR in the study of CAM-DR, so it creates the condition for the study of CAM-DR *in vitro*. Similar results were found using the same model as the FN model (Said et al., 2012). Mudry et al. (2000) found that direct interaction with stromal cells, rather than the action of soluble factors, protects leukemic cells from drug-induced apoptosis. Blockage of the vascular cell adhesion molecule-1 (VCAM-1) signaling pathway by anti-VCAM reagents abolished this protective effect, while the FN model was unable to identify whether VLA-4-mediated interactions with VCAM. The drug resistance caused by this interaction is associated with down-regulation of the pro-apoptotic molecule caspase-3 (Fortney et al., 2001). In other studies, co-culture of myeloma cells with matrix in conditioned media with soluble factors, rather than just conditioned stromal cells, protected myeloma cells from mitoxantrone drug-mediated apoptosis (Nefedova et al., 2003). However, the cell compartment culture of stromal cells and myeloma cells also produced the phenomenon of drug apoptosis protection, which further supports the interaction between tumor cells and stromal cells as an important part of drug resistance. Although the mechanism of this has not been thoroughly studied, it can be concluded that the adhesion of tumor cells to stromal cells is inseparable from cell cycle arrest and so on to avoid drug-induced apoptosis. The model diagram of CAM-DR research is shown in **Figure 2**.

In general, the interaction between the tumor microenvironment and tumor cells provides survival signals for tumor cells, regardless through direct contact or the production of soluble factors in the microenvironment. They can up-regulate anti-apoptotic molecules, down-regulate pro-apoptotic molecules, promote cell proliferation, reduce DNA damage, and increase DNA repair ability through different signaling pathways (Dehghanifard et al., 2018; Mensah et al., 2018). Therefore, the tumor microenvironment plays an integral role in tumor cell

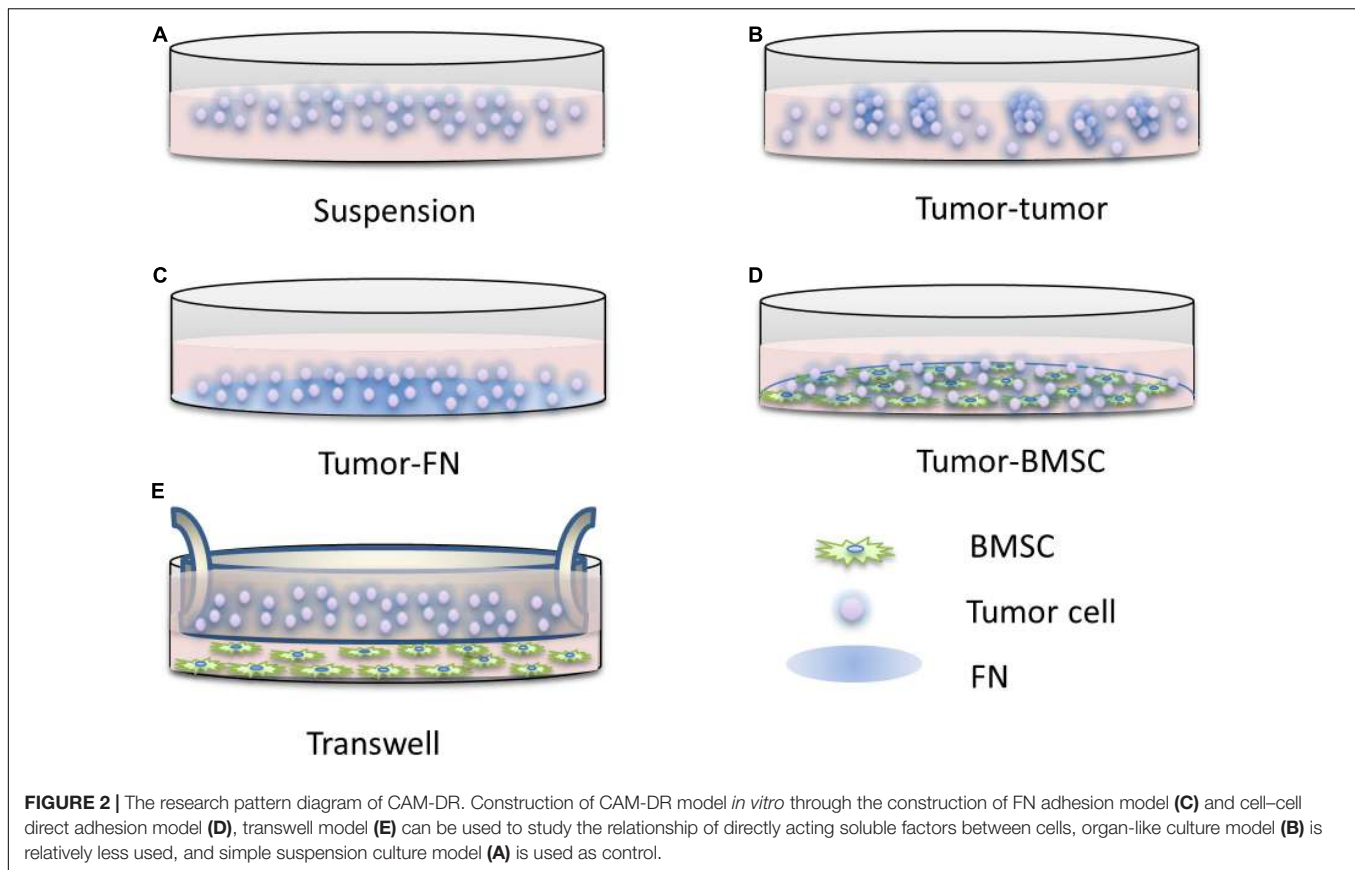
survival and drug response. The intervention of the factors that promote the growth, survival, angiogenesis, and drug resistance of tumor cells in the microenvironment will be a new therapeutic approach in the future (Naci et al., 2015). Some of these drugs have been approved for clinical use (such as Idelalisib and Dactolisib, etc.), while the others are still in clinical trials (such as Buparlisib, Dactolisib, etc.). Related inhibitors based on pre-clinical research provide new insights into the treatment of cancer and this might bring new bright prospects (Sanchez et al., 2019). The sulfonamide derivative E7820, which inhibits  $\alpha 2$  integrin subunit gene expression is used in combination with chemotherapy in phase II clinical trials in patients with various advanced or refractory malignancies (Keizer et al., 2011; Mita et al., 2011). A humanized blocking mAb against 2 integrin chains (GBR-500, Glenmark-Sanofi) has been developed and was well tolerated in phase I clinical trials. GBR-500 can block the local growth of human prostate cancer cell lines *in vivo* and increases the sensitivity of hepatocarcinoma cell lines to cytotoxic drugs (Naci et al., 2015). Targeted drugs for tumor cells and tumor microenvironment can eliminate or reduce small residual lesions of tumors and reduce acquired drug resistance.

## ROLES OF CAM-DR IN TUMORS

### Hematologic Malignancies

#### Multiple Myeloma (MM)

Multiple myeloma is the second most common hematological malignancy, accounting for about 10% of all hematological malignancies. It is characterized by abnormal proliferation of plasma cells, secretion of a monoclonal immunoglobulin or its fragments (M protein), resulting in the related organ or tissue damage. The occurrence and development of myeloma are closely related to some special changes of tumor cells, such as genomic/chromosomal instability, gene mutations, chromosome translocations, and the interaction of ECM, that is, the continuous dynamic interaction between myeloma cells and bone marrow microenvironment (Di Marzo et al., 2016). The treatment of myeloma is mainly targeted at tumor cells by chemotherapy and targeted therapy, stem cell transplantation, and symptomatic treatment. However, the 5-year survival rate of MM is about 40 months from 1990 to 2000. With the continuous development and clinical application of new drugs such as bortezomib, carfilzomib, lenalidomide, pomalidomide, and so on, the 5-year survival rate of MM has increased significantly since the beginning of the 21st century, reaching about 60 months (Furukawa and Kikuchi, 2016). Although the therapeutic drugs for MM are constantly developing, drug resistance is an important cause of death, resulting in poor prognosis, recurrence, and death. Existing studies have shown that the interaction of myeloma cells and tumor microenvironment plays an important role in the treatment of drug resistance, especially CAM-DR (Di Marzo et al., 2016; Ullah, 2019). The role of the bone marrow microenvironment is to produce a specific phenotype through the regulation of cytokines and direct contact with MM cells, resulting in insensitivity to treatment.



The molecules involved in CAM-DR in MM are commonly found in some chemokine receptors and integrins, and some cell cycle regulatory factors and apoptosis-related proteins can also be seen. The C-X-C motif chemokine receptors (CXCR) involved in CAM-DR include CXCR4, CXCR7, CXCR12 (Waldschmidt et al., 2017; Wang et al., 2019). They are classical adhesion molecules and homing factors, which are usually highly expressed on the surface of MM cells or BMSCs and can regulate cell-to-cell adhesion independently or mutually. Many upstream molecules usually regulate CAM-DR by regulating chemokine. However, MM can develop from asymptomatic to symptomatic stages, including monoclonal gammopathy of unknown significance (MGUS), smoldering multiple myeloma (SMM), MM, or plasma cell leukemia (Willenbacher et al., 2018). At the same time, CXCR is usually involved not only in CAM-DR but also in the regulation of the biological behavior of other cells, such as the maturation and development of MM cells mentioned above (Ullah, 2019). Studies have shown that in the tumor microenvironment, the adhesion of tumor cells to stromal cells can promote stromal cells to secrete high levels of IL-6, tumor necrosis factor- $\alpha$ , and osteopontin as ligands of integrins to bind and activate integrins (Damiano et al., 1999). Previous studies indicated that integrin  $\beta 1$  was highly expressed on the cell membrane in MM, and the adhesion of MM cells to ECM mediated by integrin  $\beta 1$  could significantly inhibit the apoptosis signal of caspase cells induced by chemotherapeutic drugs

(Rainero and Norman, 2015; Huang et al., 2019). Hazlehurst et al. (2000) also found that integrin  $\beta 1$  mediated cell adhesion to ECM cells significantly increased the protein level of cell cycle inhibitory protein p27<sup>Kip1</sup>, which blocked cells in the G0/G1 phase, thus escaping the killing effect of toxic drugs. The progression of tumors and the emergence of drug resistance are closely related to the NF- $\kappa$ B signaling pathway (Keats et al., 2007). The NF- $\kappa$ B signaling pathway can be activated by cytokines in the tumor cell microenvironment, or by binding to FN and secreting related factors (Landowski et al., 2003). By blocking the typical/atypical NF- $\kappa$ B pathway and hindering the degradation of I $\kappa$ B protein, bortezomib has become a standard drug in MM therapy (Murray and Norbury, 2000; Gilmore, 2007).

The adhesion of the bone marrow microenvironment in MM not only affects the apoptosis pathway and cell cycle but also leads to some other mechanisms of CAM-DR, including epigenetic mechanisms (Furukawa and Kikuchi, 2016). Previous studies have found that class I histone deacetylases (HDACs) can detect the sensitivity of proteasome inhibitors, and histone methyltransferase EZH2 can regulate the transcriptional activity of anti-apoptotic proteins activated in CAM-DR (Kikuchi et al., 2015). Besides, another histone methyltransferase MMSET can promote the repair of DNA damage and lead to drug resistance (Brito et al., 2009). With more and more in-depth research, more molecular markers have been discovered and studied in the CAM-DR of MM, including microRNAs (miRNAs/miRs)

(Wang et al., 2011; Wu et al., 2019), exosomes, and cancer-associated fibroblasts (CAFs) (Di Marzo et al., 2016). The disruption of fibronectin-heparan sulfate interactions blocks exosome binding to MM cells or BM stromal cells, highlighting a specific cross-talk fostered by exosomes in the bone marrow microenvironment (Thompson et al., 2013). CAFs can also serve the function of modifying the bone marrow stroma, influencing chemotaxis, adhesion, proliferation, and apoptosis caused by CAM-DR and the expression of adhesion molecules (Frassanito et al., 2014). This article summarizes the CAM-DR of MM (see **Table 1**).

### Non-hodgkin's Lymphoma (NHL)

Non-Hodgkin's lymphoma is a group of malignant tumors originating from lymph nodes and extranodal lymphoid tissues, accounting for more than 90% of all lymphomas, including B-cell and NK/T-cell lymphomas. Due to the high heterogeneity of lymphoma, there are more than 60 subtypes of lymphoma, ranging from low-grade malignancy to highly invasive (Li Y. et al., 2015). The malignant degree of T-cell lymphoma is more aggressive than B-NHL, and the treatment lacks specificity. The clinical diagnosis and treatment of B-NHL strictly follow the standard clinical guidelines, but unfortunately, the wide use of monoclonal antibodies has not significantly improved the prognosis of NHL (Lwin et al., 2007b). Based on the recent advances into the tumor microenvironment of NHL, it revealed that CAM-DR is also a crucial factor leading to the recurrence and death (Burger et al., 2009). Studies confirmed that lymphoma cells adhere to BMSCs in the tumor microenvironment to produce a multi-drug resistance (MDR) phenotype, and interrupting this cell adhesion-mediated signal can significantly enhance the sensitivity of tumor cells to chemotherapeutic drugs. When the normal adhesion between malignant tumor cells and the ECM is lost, tumor cells are prone to apoptosis, which is called "anoikis" (Alderton, 2015).

In the related researches of CAM-DR in NHLs, the expressions and functions of characteristic molecules were similar. Despite the common pathological types, there are rare pathological types involving Burkitt's lymphoma (BL) and mantle cell lymphoma (MCL). Adhesion molecules such as surface chemokine receptors CXCR4, CXCR5, and CXCR7 (Kurtova et al., 2009; Xargay-Torrent et al., 2013) and integrin family molecule Integrin  $\alpha 4\beta 1$  (Takeda et al., 2020) make tumor cells home and stay in matrix niches to escape the killing effect of drugs. Eke and Cordes (2015) found that the signal cascade mediated by integrins and the changes of cell cycle and apoptosis are the main mechanisms of CAM-DR production. The anti-CD49d monoclonal antibody or polypeptide that competitively binds with Integrin $\alpha 4/CD49d$  ligand can inhibit the adhesion of malignant B-NHL cells to stromal cells and enhance the activity of cytotoxic drugs (Takeda et al., 2020).

Due to the diversity of pathological types in lymphomas, the interactions between abnormally expressed molecules are also complex, which also play cross roles in the biological behaviors of NHLs. In particular, they have different regulations on the proliferation of tumor cells. The expression of some molecules can promote the proliferation of tumor cells, and at the same

time, CAM-DR is a positive factor of poor prognoses, such as ADAM12, FBP1 (Huang et al., 2016; Yin et al., 2017). Although the expression of some molecules can reduce the proliferation of tumor cells, the production of CAM-DR is consistent with the clinical practice that is not sensitive to the treatment of inert lymphomas, such as DYRK2 (Wang et al., 2015). Some molecules express the proliferation of tumor cells while producing CAM-DR, which is consistent with the clinical practice that is not sensitive to the treatment of indolent lymphomas, such as DYRK2. Some molecules can reverse CAM-DR and promote proliferation, which is the research direction of clinical targeted therapeutic intervention, such as CKIP-1 and SGTA (Wang et al., 2014; Zhu et al., 2017). The relevant summary is shown in **Table 2**.

### Leukemia

Leukemia is a disease characterized by abnormal tumor proliferation of cells in the hematopoietic system and extensive infiltration of extramedullary organs, and abnormal proliferation, differentiation, and apoptosis of peripheral blood leukocytes. It can be divided into different disease types according to the course of the disease, cell morphology, chromosome abnormality, and so on. The specific leukemia subtypes of interest were acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), and CML (Li et al., 2021). Chemotherapy remains the main treatment of leukemia. With the development of stem cell transplantation technology in recent years, the treatment and prognosis of leukemia have been improved significantly. However, chemotherapy resistance is still a problem that cannot be ignored, which directly leads to insensitivity to first-line treatment or recurrence after short-term remission. The classic drugs for the treatment of leukemia are cell-cycle non-specific killing drugs, which do not have the characteristics of targeted killing of tumor cells. Although the research of targeted drugs is continuously deepening, however, there is still no breakthrough in disease control and prognosis. In contrast, the molecular interaction between the microenvironment and leukemic cells is often ignored (Ruan et al., 2020). Similar to previous myeloma and lymphoma, the tumor microenvironment plays a key role in the treatment of leukemia (Wang et al., 2018; Heath et al., 2019).

Chemotherapeutic resistance in adults with ALL is still an insurmountable problem (Roboz et al., 2014). Although the survival rates of childhood ALL are improving, the recurrence of disease after chemotherapy is still unsolved (Bhojwani et al., 2015). El Azreq et al. (2012) report that collagen/ $\beta 1$  integrin signaling inhibits doxorubicin-induced apoptosis of leukemic T-cells by up-regulating the expression of the ATP-binding cassette C 1 (ABCC1) transporter. Their results indicate for the first time that collagen/ $\beta 1$  integrin/ERK signaling activation could represent a key pathway in T-ALL chemoresistance. In CLL, it has been reported that CAM-DR can activate the phosphatidylinositol 3-kinase (PI3K)/AKT signal pathway, which in turn leads to proliferation (Hoellenriegel et al., 2011). *In vitro* experiments showed that PI3/Akt signaling pathways were related to poor prognosis and drug resistance, and the reduction

**TABLE 1** | CAM-DR in MM.

Molecules	Expression level	Biological functions	Signaling pathways	References
ANXA7/CDC5L	Up	Promote the cell cycle, proliferation, and CAM-DR		Liu et al., 2020
BTK/CXCR4	Up	Relate to MM progression and drug resistance		Wang et al., 2019
p-EZH2	Up	p-EZH2(S21) induce hypermethylation of H3K27, lead to the sustained expression of antiapoptotic genes	IGF-1R/PI3K/AKT	Kikuchi et al., 2015
CXCL12/CXCR7	Up	Enhance CAM-DR	ERK/MAPK	Waldschmidt et al., 2017
Integrin $\alpha$ 6 $\beta$ 1	Up	An autocrine mechanism in CAM-DR	Wnt3/RhoA/ROCK	Kobune et al., 2007
Integrin $\beta$ 7	Up	Enhance CAM-DR, migration, and BM homing	NF- $\kappa$ B	Neri et al., 2011
Integrin $\alpha$ 4 $\beta$ 1	Up	CAM-DR and inhibit cell apoptosis	NF- $\kappa$ B	Fontana et al., 2021; Sevilla-Movilla et al., 2020
Numb/Integrin $\beta$ 1	Up	Regulate cell-cycle progression	PI3K/AKT	Huang et al., 2019
p27	Up	Regulate cell-cycle progression		Hazlehurst et al., 2000; Zhan et al., 2007
PDCD4	Down	Confer drug resistance via enhancing AKT phosphorylation at Ser473		Wu et al., 2019
CHD1L AGS3	Up	Anti-apoptotic	Caspase-9/3	Shao et al., 2014; Xu et al., 2016
EphA4	Up	Promote proliferation via the regulation of cell cycle and CAM-DR by enhancing p-AKT expression		Ding et al., 2017
Kpn $\beta$ 1	Up	Associate with the proliferation, interact with p65, and promote CAM-DR	NF- $\kappa$ B	He et al., 2016
RBQ3 ARF1 VPS4B PKM2 GPR37 RUNX2	Down	Promote proliferation, knockdown of molecules induced CAM-DR	PI3K/Akt MAPK/ERK	Huang et al., 2014; He Y. et al., 2015; Tang et al., 2015; Liu et al., 2016; Xu et al., 2017; Zhang et al., 2020
Homer1b/c	Down	Pro-apoptotic		Tang et al., 2016

of apoptosis caused by regulatory chemotherapy in pediatric pre-B ALL (Morishita et al., 2012). In CLL and AML, inhibition of the PI3K/AKT pathway can lead to a decrease in cell proliferation (Billottet et al., 2006; Nguyen et al., 2014). Among the studies of CAM-DR in the hematological tumors mentioned above, it has been found that PI3K/AKT is involved in the occurrence and development of CAM-DR in MM and NHL (Ouyang et al., 2016; Huang et al., 2019). Moreover, in the solid tumor, adhesion-mediated activation of the PI3K/AKT pathway has also been reported (Zhu et al., 2012; Toth et al., 2019). Due to the relations between PI3K activation and the unlimited proliferation of tumor cells and CAM-DR, PI3K/AKT has become a promising target in anti-tumor therapies. As part of the combined treatment, the PI3K inhibitors can not only inhibit tumor cell proliferation but also restore sensitivity to other treatments, reduce the occurrence of drug resistance and achieve a synergistic killing effect. Further studies on PI3K/AKT signaling pathway inhibitors have found

that inhibition of related signaling pathways can significantly inhibit tumor cell proliferation and enhance chemosensitivity in CLL and AML (Billottet et al., 2006; Nguyen et al., 2014). Some results showed that by inhibiting pro-apoptotic Ras-related C3 botulinum toxin substrate 1 (Rac1),  $\alpha$ 2 $\beta$ 1 integrin can be a major pathway protecting leukemic cells from genotoxic agents and may thus represent an important therapeutic target in the anti-cancer treatment of AML (Naci et al., 2019). Bruton tyrosine kinase (BTK) inhibitors have also been found to reverse CAM-DR and tumor migration in CML (de Rooij et al., 2012). Fernandez-Vidal et al. (2006) have shown that the inhibition of proliferation and anti-apoptosis induced by adhesion is related to the expression of M-phase inducer phosphatase 1 (CDC25A), while CDC25A participates in the regulation of the cell cycle and activates the PI3K/AKT signal pathway. CDC25A is a bispecific phosphatase, which mainly participates in the G1-S transition of the cell cycle, and plays an important role in the

**TABLE 2** | CAM-DR in NHL.

Tumor type	Molecules	Expression level	Biological functions	Signaling pathways	References
MCL	SOX11	Up	Increase migration, transmigration, proliferation, and resistance	FAK/PI3K/AKT p38/MAPK	Balsas et al., 2017; Yang et al., 2020
MCL	CXCL12/CXCR7	Up	Enhance CAM-DR and migration		Kurtova et al., 2009; Xargay-Torrent et al., 2013
BL	CD49D/E	Up	Enhance CAM-DR	NF- $\kappa$ B	Takeda et al., 2020
DLBCL	HGF/MET	Up	Induce integrin-mediated adhesion	RAS/MAPK PI3K/PKB	Tjin et al., 2006
DLBCL	ABCG2	Up	Increase expression of the antiapoptotic proteins		Singh et al., 2011
B-NHL	Integrin $\alpha$ 4 $\beta$ 1	Up	CAM-DR and inhibit cell apoptosis		Mraz et al., 2011
B-NHL	PRMD1 topoisomerase II $\beta$ MDR1	Up	Enhance CAM-DR		Hazlehurst et al., 2006; Lin et al., 2011; Yagi et al., 2013
B-NHL	BAFF hPEBP4	Up	Anti-apoptotic		Lwin et al., 2009; Wang et al., 2013
NHL	p27	Up	Regulate cell-cycle arrest		Lwin et al., 2007a
NHL	XIAP	Up	Anti-apoptotic	NF- $\kappa$ B	Lwin et al., 2007b
NHL	HRF/TCTP	Up	Anti-apoptotic and enhance CAM-DR		He S. et al., 2015
NHL	microRNA-181a	Up	Enhance CAM-DR		Lwin et al., 2010
NHL	TRIP6 CKIP-1 SGTA	Down	Promote proliferation, knockdown of molecules induced CAM-DR	PI3K/AKT	Wang et al., 2014; Miao et al., 2016b; Zhu et al., 2017
NHL	DIXDC1 YB-1 ENO1 Sam68 ADAM12 FBP1	Up	Promote proliferation and CAM-DR	PI3K/AKT	Wu et al., 2015; Zhu X. et al., 2015; Huang et al., 2016; Miao et al., 2016a; Ouyang et al., 2016; Yin et al., 2017
NHL	DYRK2	Up	Decrease proliferation but enhance CAM-DR		Wang et al., 2015

regulation of the cell cycle involving CAM-DR. Previous shreds of evidence suggested that integrins play key roles in the CAM-DR of MM and NHL, and existing studies also indicated that integrin  $\alpha$ 4 plays a similar role in leukemia's drug resistance (Shishido et al., 2014). Incomplete sensitivity to chemotherapy leads to the persistence of some drug-resistant cells and minimal residual diseases (MRD) (Akabane and Logan, 2020). Interfering integrin  $\alpha$ 4-mediated cell adhesion can make them sensitive to chemotherapy, thus further promoting the killing effects of all tumor cells in an MRD setting.

## Solid Tumors

The incidence of hepatocellular carcinoma (HCC) is high in Asia. Only about 20% of patients have the chance of surgical resection, and most patients have a short-term risk of recurrence after surgery (Saito et al., 2019). Despite the development of interventional therapy, targeted therapy, and immunotherapy,

the overall prognosis of HCC is still poor and it remains the second leading cause of cancer-related deaths in the world (Ferlay et al., 2015). Moreover, most HCCs are resistant to chemotherapeutic drugs (Wu et al., 2021). With the continuous study of the tumor microenvironment, it is found that CAM-DR in HCC is similar to hematological tumors. In previous studies, it has been found that the adhesion of HepG2 cells to FN can significantly increase the drug resistance of tumor cells, and is closely related to the expression of integrin  $\beta$ 1 (Zhu et al., 2012). At the same time, some studies have shown that the regulation of connective tissue growth factor (CTGF) and collagen 1A1 (COL1A1) is involved in CAM-DR (Song et al., 2017).

In addition to HCC, CAM-DR is also being investigated in many epithelial tumors. CAM-DR can occur in almost all kinds of tumors. Nakagawa et al. (2014) found that the involvement of integrin  $\beta$ 1 in the adhesion of tumor cells to FN can lead to 5-Fu resistance in the study of oral squamous cell carcinoma (OSCC).



In head and neck cancer, a melphalan-resistant nasopharyngeal carcinoma (NPC) cell line shows up-regulation of integrin subunits  $\alpha 2$ ,  $\alpha 5$ ,  $\alpha 6$ ,  $\beta 1$ , and  $\beta 2$  compared with drug-sensitive parent lines. As well as chemoresistance phenotype, this was associated with a significantly stronger binding to ECM and increased invasiveness (Liang et al., 2001). A vinblastine-resistant subline of renal carcinoma cells showed increased expression of integrin very late antigen-1/2 and decreased expression of integrin very late antigen-6 in association with increased attachment to collagen and FN (Duensing et al., 1996). Similar results have been found in gastric cancer (GC). MGr1-Ag/37LRP (P37-kDa laminin receptor precursor) can promote CAM-DR by activating downstream focal adhesion kinase (FAK)/PI3K and mitogen-activated protein kinase (MAPK) signal pathways through interaction with laminin (Sun et al., 2014b). Common intracellular signals related to integrin binding primarily start with the activation of FAK, recruitment, and activation of Src kinase family, followed by PI3K/Akt pathway or Ras/RAF/MEK/ERK signaling axis, resulting in increased invasion and survival (Li W. et al., 2015; Hou et al., 2016). The mechanistic impact of integrin on chemosensitivity showed high diversity, and a significant increase in MAPK and CREB signal pathways could be found in CAM-DR (Jakubzig et al., 2018). In other words, integrin-mediated matrix binding induces crosstalk with the growth factor signal axis, such as EGFR via FAK or MAPK/ERK pathways triggering proliferation and reducing apoptosis (Jeanes et al., 2012). Although the mechanism of the MAPK/ERK signaling pathway is still relatively thorough compared with the above two pathways, the research of corresponding inhibitors is also relatively small, but it is also believed to be a research direction of the targeted treatment of drug resistance in the future. When human breast cancer cell lines MCF-7 and MDA-MB-231 bind to collagen type 1 (COL1) or FN, they are less sensitive to the cytotoxicity of cisplatin, doxorubicin, and mitoxantrone. CAM-DR is also closely related to the regulation of integrin  $\beta 1$  in breast cancer (Baltes et al., 2020). The expression of integrin  $\beta 1$  also plays an important role in CAM-DR and is considered to be a potential target for non-small cell lung cancer (NSCLC) (Wang et al., 2020). Adhesion of small-cell lung cancer (SCLC) cells to ECM enhances tumorigenicity and confers resistance to chemotherapeutic agents as a result of  $\beta 1$  integrin-stimulated tyrosine kinase activation suppressing chemotherapy-induced apoptosis (Sethi et al., 1999). Strategies based on blocking  $\beta 1$  integrin-mediated survival signals may represent a new therapeutic approach to improve the response to chemotherapy in SCLC (Rintoul and Sethi, 2001). In some special types of tumors, researches on CAM-DR have also been conducted, such as glioblastoma multiforme (GBM) and glioma, blocking the interaction between tumor cells and microenvironment can reverse the drug resistance (Westhoff et al., 2008; Ding et al., 2020).

In human reproductive system tumors, hormone receptor-dependent diseases can be treated with endocrine drugs and/or potential treatments. In reproductive system-related tumors, the primary and acquired drug resistance of endocrine and chemotherapeutic drugs have become the hotspots of current researches (Buttigliero et al., 2015; Lin et al., 2019). In

bone-metastatic castration-resistant prostate cancer (CRPC), the interaction between tumor cells and microenvironment combined with hypoxia can lead to the continuous activation of the PI3K signaling pathway, which eventually leads to drug resistance. CAM-DR is mainly regulated by Integrin  $\alpha 6\beta 1$ , while hypoxia is related to the regulation of PIM kinase in CRPC (Toth et al., 2019). In ovarian cancer, the expression of Lewis  $y$  is significantly high, and it is positively correlated with the expression of some adhesion molecules. The adhesion molecules integrin  $\alpha 5$  and integrin  $\beta 1$  can be used as independent prognostic factors to judge progression-free survival (PFS) and overall survival (OS) in ovarian cancer (Zhu L.C. et al., 2015). Lewis  $y$  inhibits apoptosis and increases CAM-DR in ovarian cancer mainly by activating the FAK signal pathway and inhibiting the BCL-2/BCL-XL pathway (Yan et al., 2015). The above studies on CAM-DR in solid tumors are summarized in **Table 3**.

## THERAPEUTIC DRUGS AND CLINICAL APPLICATION

### Inhibitors

With the deepening of CAM-DR studies, there are more and more studies on inhibitors. Reversing CAM-DR can significantly improve drug resistance, reduce recurrence, improve the prognosis of patients, and provide a leap forward in clinical treatment. At present, there are some difficulties in targeting molecules. Although there are significant differences in expression, they lack specificity. Some monoclonal antibodies have been proven to be effective in reversing CAM-DR, and the combined use of traditional Chinese medicine can often inhibit the CAM-DR phenomenon. Most studies and clinical applications are related to signal pathway inhibitors (see **Table 4** for details).

It has been made clear that the occurrence of CAM-DR is closely related to the activation of related signal pathways, and there are more and more studies on inhibitors of signal pathways. More sophisticated inhibitors of the PI3K/AKT signaling pathway compared to others. In the *in vitro* experiment, the addition of PI3K inhibitor can significantly reduce the proliferation of tumor cells, reduce the adhesion of tumor cells to the microenvironment, and reverse drug resistance. In the treatment of hematological malignant tumors, the research of PI3K inhibitors presents different stages. The inhibitors approved by FDA are idelalisib, copanlisib, and duvelisib. Idelalisib, also known as CAL101, was approved for inert non-Hodgkin's Lymphoma (iNHL) in July 2014 (Miller et al., 2015). The approval is based on the results of a single-arm phase II study in which the overall remission rate (ORR) of idelalisib in patients with follicular lymphoma (FL) and small lymphocytic lymphoma (SLL) was 54 and 58%, respectively (Furman et al., 2014; Gilbert, 2014). Copanlisib is the second PI3K inhibitor approved for recurrent FL patients by the FDA in September 2017 (Mensah et al., 2018; Tang et al., 2018). Compared with Idelalisib, the high affinity for the p110 subunit of PI3K makes it provide higher specificity and lower gastrointestinal toxicity (Krause et al., 2018).

**TABLE 3** | Roles and mechanisms of CAM-DR in solid tumors.

Tumor type	Molecules	Biological functions	Signaling pathways	References
OSCC	FN	Enhance chemosensitivity to 5-FU and apoptosis	ILK/Akt/NF- $\kappa$ B	Nakagawa et al., 2014
NPC	Integrin subunits $\alpha$ 2, $\alpha$ 5, $\alpha$ 6, $\beta$ 1, and $\beta$ 2	Chemoresistance phenotype and increase invasiveness		Liang et al., 2001
HCC	CTGF/COL1A1	Form of compact spheroids and evade anticancer therapies		Song et al., 2017
HCC	Integrin $\beta$ 1	Decrease apoptosis	PI3K/AKT	Zhu et al., 2012
Bone-metastatic CRPC	Integrin $\alpha$ 6 $\beta$ 1/PIM	Promote survival by reducing oxidative stress and preventing cell death	PI3K/mTOR	Toth et al., 2019
GC	MGr1-Ag/37LRP	Ligation-induced adhesion participated in protecting cells from some apoptotic stimuli caused by chemotherapeutic drugs	FAK/PI3K and ERK/MAPK	Liu et al., 2010; Sun et al., 2014a,b
Ovarian cancer	Lewis y	Enhance CAM-DR	FAK	Yan et al., 2015; Zhu L.C. et al., 2015
Breast cancer	Integrin $\beta$ 1	Transmits breast cancer cells into chemoresistance	ERK/MAPK	Baltes et al., 2020
Breast cancer	Integrin $\beta$ 1	Inhibits drug-induced apoptosis by inhibiting the release of cytochrome c from the mitochondria	PI3K/AKT	Aoudjit and Vuori, 2001
NSCLC	Integrin $\beta$ 1	Increase cell viability, promote migration and adhesion		Wang et al., 2020
SCLC	Integrin $\beta$ 1	G2/M cell cycle arrest by up-regulate p21 <sup>Cip1/WAF1</sup> and p27 <sup>Kip1</sup> and the down-regulate of cyclins E, A, and B; prevents etoposide-induced caspase-3 activation and subsequent apoptosis	PI3K/AKT	Hodkinson et al., 2006, 2007
GMB		Mode of CAM-DR by forming spheres via cell-cell interactions	Raf/MEK/ERK and PI3K/AKT	Westhoff et al., 2008
Glioma	$\beta$ -catenin	Enhance cell adhesion contributed to the insensitivity to Temozolomide	IP3R1/AKT/ $\beta$ -catenin	Ding et al., 2020

Clinical trials of copanlisib are performed in multiple subtypes of NHL in order to further expand its clinical indications. Duvelisib (also known as ABBV-954, INK-1197, and IPI-145) is an oral PI3K inhibitor for the treatment of hematological malignant tumors (Flinn et al., 2018a,b). In September 2018, FDA approved duvelisib for more than two lines of treatment for patients with recurrent/refractory FL and CLL/SLL (Blair, 2018; No author list, 2018). The approval of the FDA is based on the improvement of survival and treatment efficacy of phase III DUO and phase II DYNAMO trials. In the DUO study, the median PFS of CLL/SLL patients receiving drug treatment was 16.4 months and ORR was 78%. In contrast, patients who received CD20 monoclonal antibodies had a median PFS of 9.1 months and an ORR of 39% (Flinn et al., 2018a). Currently, the researchers are dedicating to

develop more PI3K pathway inhibitors, and some inhibitors are also in preliminary clinical trials or *in vitro* experiments, such as Buparlisib (BKM120) and Dactolisib (BEZ235) (Ragon et al., 2017; Stefanzi et al., 2017). While improving the curative effect, we should also pay more attention to the side effects caused by the inhibitors.

Compared with PI3K inhibitors, NF- $\kappa$ B pathway inhibitors have been widely used in MM, such as bortezomib (BTZ), which induces apoptosis by inhibiting the degradation of I $\kappa$ B $\alpha$  and inhibiting the activation of NF- $\kappa$ B in cancer cells (Murray and Norbury, 2000). As a small molecule NF- $\kappa$ B signal inhibitor, V1810 directly inhibits NF- $\kappa$ B by non-relying on the proteasome mechanism to induce apoptosis of MM cells (Kurland et al., 2001). P38 MAPK inhibitor SB203580

**TABLE 4** | Overview of the targeting drugs.

Classification	Name	Disease	Target	Mechanism	Phase	References
CXCR4 inhibitors	Plerixafor (ADM3100) BKT140	MM and MCL	CXCR4/CXCL12	CXCR4 antagonist; abrogate CXCL12 induced receptor internalization; induce MM cell apoptosis	Clinical trial	Kurtova et al., 2009; Balsas et al., 2017; Waldschmidt et al., 2017; Wang et al., 2019
Anti-integrin antibody	Natalizumab	MM, MCL, and B-NHL	Integrin $\alpha 4\beta 1/7$	Non-competitive antagonism	FDA approve	Kobune et al., 2007; Mraz et al., 2011; Xargay-Torrent et al., 2013
	E7820 GBR-500	HCC	Integrin $\alpha 2$	Block the local growth and increases the sensitivity of cancer cell lines to cytotoxic drugs	Phase II clinical trials	Keizer et al., 2011; Mita et al., 2011; Naci et al., 2015
VLA4-nanoparticles	V-NP/V-CP	MM	Integrin $\alpha 4\beta 1$	V-CP: anti-myeloma effects. V-CP: further reduced tumor burden and prolonged survival without adding to toxicity.	<i>In vitro</i>	Fontana et al., 2021
Selectin inhibitors	Uproleselan (GMI-1271)	AML	E-selectin	Small molecule inhibitor against E-selectin on endothelial cells	<i>In vitro</i>	Barbier et al., 2020
PI3K inhibitors	Idelalisib Copansilib Duvelisib Apelisib (BYL719)	Leukemia breast cancer	PI3K	Inhibit PI3K/AKT signaling pathway	FDA approve	Miller et al., 2015; Flinn et al., 2018a,b; Mensah et al., 2018
	Buparlisib (BKM120) Dactolisib (BEZ235)	Leukemia	PI3K	Inhibit PI3K/AKT signaling pathway	Phase I clinical trials	Ragon et al., 2017; Stefanzi et al., 2017
	LY294002	MM, NHL, bone-metastatic CRPC, SCLC	PI3K	Inhibit PI3K/AKT signaling pathway	<i>In vitro</i>	Aoudijt and Vuori, 2001; Xu et al., 2017; Huang et al., 2019; Toth et al., 2019
AKT inhibitors	MK2206 PF-04691502 A6730	MM and NHL	AKT	Inhibit PI3K/AKT signaling pathway	<i>In vitro</i>	Wu et al., 2015; Ding et al., 2017; Zhang et al., 2020
MAPK inhibitor	PD98059 SB203580	MM and MCL	MAPK	ERK/MAPK signaling pathway inhibitors	<i>In vitro</i>	Balsas et al., 2017; Xu et al., 2017; Yang et al., 2020
ABCG2/BRCP inhibitor	Fumitremorgin	DLBCL	ABCG2/BRCP	Abrogate the stroma-induced chemotolerance	<i>In vitro</i>	Singh et al., 2011
Cycloamine derivative	Cycloamine-KAAD	DLBCL	Hedgehog signaling	Inhibit hedgehog signaling	<i>In vitro</i>	Singh et al., 2011
Nanomedicine	PDGFR- $\beta$ - doxorubicin	Tumors	Hedgehog signaling	Increase the binding of doxorubicin and reduce the free doxorubicin	<i>In vitro</i>	Prakash et al., 2010
Others	FNIII14	OSCC	FN	Enhance chemosensitivity to 5-FU and apoptosis	<i>In vitro</i>	Nakagawa et al., 2014
	Losartan	HCC	CTGF/COL1A1	Decrease the form of compact spheroids	<i>In vitro</i>	Song et al., 2017
	Oroxilin A	HCC, glioma	$\beta$ -catenin	inhibit IP3R1/AKT/ $\beta$ -catenin pathway	<i>In vitro</i>	Zhu et al., 2012; Ding et al., 2020
	Wenxia Changfu formula (WCF) Carbenoxolone	NSCLC GMB	Integrin $\beta 1$	Decrease cell adhesion Sensitize to CD95-induced apoptosis	<i>In vitro</i>	Wang et al., 2020 Westhoff et al., 2008

can inhibit tumor microenvironment-induced proliferation in MCL *in vitro* (Yang et al., 2020). Although FAK inhibitor (PF) only reduces cell chemotaxis and *trans*-endothelial migration, the potential ability to prevent tumor cells from bone marrow and lymph node microenvironment protection by recirculation makes it a synergistic drug of AnticD20 or BTZ (Balsas et al., 2017). Strategies designed to target down-stream of cell adhesion molecules such as FAK or integrin linked kinase may eliminate concerns of redundancy of adhesion-mediated signaling. Similarly, inhibiting the Janus-activated kinase (JAK)/signal transduction and activator of transcription (STAT) pathway for cytokine signaling maybe more effective comparing to the blockade of a single cytokine receptor (Chen et al., 2020).

## Nanomedicine Therapeutic

Nanomedicine is an emerging form of treatment, which focuses on the delivery of alternative drugs and improvement of therapeutic effects, while reducing harmful side effects on normal tissues. The novel nanomedicines based on the tumor genetic spectrum can design and produce drugs flexibly and quickly, which makes the drug selection of personal treatment more centralized and effective (Khot et al., 2021). With the advanced design and alternative drug delivery mechanisms of different nanodrugs (including liposomes, dendrimers, micelles, carbon-based, polymer conjugates, and metal nanoparticles), overcoming various forms of multidrug resistance looks promising and opens up a new field of vision for cancer treatment (Markman et al., 2013). For example, a unique nano-carrier was made using albumin and a platelet-derived growth factor receptor- $\beta$  (PDGFR- $\beta$ ) recognizing cyclin peptide conjugated to doxorubicin through an acid-sensitive hydrazone linkage. *In vivo*, the binding of doxorubicin can be increased, and the free doxorubicin can be reduced, thereby reducing the expression of PDGFR- $\beta$ , significantly reducing tumor growth (Prakash et al., 2010). A large number of unique nanodrugs have been created and widely studied, and have entered the stage of clinical development. With more discoveries and drug optimization, the advantages of nanodrugs over current treatment options will continue to be enhanced, thus effectively eradicate drug-resistant cancers.

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## CONCLUSION AND PROSPECTS

In the continuous improvement of tumor clinical treatment, drug resistance has become a non-negligible hotspot, which is a key factor for successful treatment. With the advancement and improvement of clinical treatment technology, overcoming drug resistance has become a key issue to improve treatment effect and prognosis of patients. CAM-DR is an important factor in drug resistance caused by the tumor microenvironment. A large number of studies are focusing on CAM-DR, covering hematologic malignant tumors to solid tumors, and the mechanisms insight are gradually being revealed. According to these mechanisms, the study of corresponding inhibitors and combined therapies can reverse the occurrence of drug resistance to a great extent. However, the mechanism of CAM-DR is very complex, involving the activation of multiple signal pathways, and the development of corresponding inhibitors and clinical trials are also underway, which is expected to improve the existing treatment to a higher level in the future. With the deepening of CAM-DR research, we believe that overcoming CAM-DR can provide a new method for tumor treatment. Taken together, previous studies demonstrate that CAM-DR is crucial in the drug resistance mechanisms and reversing CAM-DR might provide a promising therapeutic strategy for clinicians.

## AUTHOR CONTRIBUTIONS

YH and YW collected the related article and finished the manuscript and figures. SJ and SH gave constructive guidance and made critical revisions. XS participated in the design of this review. JT and SQ revised the manuscript. All authors read and approved the final manuscript.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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