REVIEW

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CD44: a potential therapeutic target in chronic myeloid leukemia

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Development of tyrosine kinase inhibitors (TKIs) achieved great success in the treatment of chronic phase chronic myeloid leukemia (CML). However, patients with CML still relapse without taking TKIs and cases in the accelerated phase or aggressive blast crisis rarely achieved deep response to TKIs. Drug resistance and persistence of leukemia stem cell (LSC) remain great challenges. BCR-ABL kinase dependent or independent mechanism of action are still far from being understood. To achieve a stable deep molecular response and treatment-free remission, finding new targets, eliminating LSC, reducing recurrence and improving prognosis are problems urgently to be solved. It is revealed that tumor microenvironment is crucial for survival, invasion and metastasis of tumor cells. As an adhesion molecule, CD44, a single-chain transmembrane glycoprotein, is not only being identified as a marker for cancer stem cells, but also plays a crucial role in microenvironmental communication and transmitting intracellular signaling for cell proliferation, differentiation, migration, and contributes to tumorigenesis. In this review, we focus on current data relevant to CD44, and outline CD44 structure, the regulation of CD44, functional properties of CD44 in survival, resistance, CML stem cells as well as the potential CD44-targeting therapy for CML management.

1. Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative hematopoietic stem cell disorder characterized by the proliferation and accumulation of mainly mature myeloid cells in the peripheral blood, bone marrow and spleen (Apperley 2015). Most patients with CML are diagnosed in the chronic phase (CP) characterized by overproduction of normal myeloid cells. If untreated or without effective therapy, CP-CML will progress into the accelerated phase (AP) or blast crisis (BC) with a decrease in the differentiation capacity of the cells, losing response to regular factors and transforming to acute leukemia, more often, acute myeloid leukemia (Faderl et al. 1999; Rosenthal et al. 1977). Translocation of chromosomes 9 and 22 gives rise to the Philadelphia (Ph) chromosome, which can be detected in more than 90% of CML patients (Rowley et al. 1973). Chromosome translocation produces the *BCR-ABL1* fusion gene, which encodes the fusion protein in Ph positive CML cells. This oncoprotein acquires dysregulated tyrosine kinase activity that could continuously phosphorylate the downstream signaling pathways and finally leading to the malignant transformation of cells (Shtivelman et al. 1985; Ren et al. 2005).

Development of tyrosine kinase inhibitors (TKIs) achieved great success in the treatment of CP-CML. But none of the currently approved first or second-generation TKIs has shown clinically significant differences in long-term progression-free survival (Liu et al. 2016; Kantarjian et al. 2012; Hochhaus et al. 2016; Cortes et al. 2012, 2018). Moreover, patients still relapse without taking TKIs, and either AP-CML or BC-CML rarely achieve deep response to TKIs (Druker et al. 2001; Jones et al. 2008; Hochhaus et al. 2020). New targets of treatment for CML should achieve a stable deep molecular response (DMS) and treatment-free remission (TFR) (Hochhaus et al. 2020). However, drug resistance, leukemia stem cell (LSC) persistence and disease progression remain great challenges in clinical and mechanisms involved are still far from being understood (Rinke et al. 2020; Houshmand et al. 2019). Accordingly, there is an urgent need for novel therapeutic targets in combination with or without TKIs in order to overcome those thorny issues, reduce recurrence and finally improve prognosis.

It is revealed that tumor microenvironment is crucial for survival, invasion and metastasis of tumor cells (Schulz et al. 2019; Scielzo et al. 2020; Wang et al. 2013). Cross-talk between stem cells and their surrounding extracellular matrix (ECM) through a number of cell surface receptors like integrins, membrane-bound glycoproteins determines the fate of stem cells (Gattazzo et al. 2014; Zöller 2015). Being an adhesion molecule, CD44 is a transmembrane glycoprotein that expresses in normal and tumor cells and is being detected as a surface biomarker of cancer stem cells (CSCs), individually or in combination with other markers such as CD24, CD133 and CD34 for identifying CSCs in various types of cancer (Yan et al. 2015, Takaishi et al. 2009). CD44 not only plays an important role in physiological processes such as hematopoiesis and lymphocyte homing (Ponta et al. 2003), but also participates in tumor behaviors like survival, invasion, chemoresistance and progression (Wang et al. 2019a,b; Zanjani et al. 2018). In addition, CD44 can interact with kinds of ECM components such as hyaluronan (Bourguignon 2019), osteopontin (OPN) (Wei et al. 2017), matrix metalloproteases (MMPs) (Lee et al. 2019), fibronectin (Wirth et al. 2020), serglycin (Chu et al. 2016), cytokines and messenger molecules (Orian-Rousseau and Sleeman 2014). Accordingly, CD44 plays a crucial role in microenvironmental communication and transmitting intracellular signaling for cell proliferation, differentiation, migration, and contributes to tumorigenesis and metastasis (Karousou et al. 2017; Chen et al. 2018a; Senbanjo and Chellaiah 2017).

In CML, potential CD44 contributions to the pathophysiology have been discussed; however, the underlying biological mechanisms remain elusive. With some aspects controversially described, it has become necessary to further examine and more deeply understand the role of CD44 in this disease. In this review, we discuss the roles of CD44 in CML cell proliferation, resistance, LSCs and its suitability for therapeutic exploitation.

2. Structure of CD44

CD44 is a single-chain transmembrane glycoprotein encoded by a single gene on chromosome locus 11p13 containing 19 exons in humans (Screaton et al. 1992). The first five exons (1 to 5) and the last five exons (16 to 20) of CD44 gene encode CD44 standard (CD44s) isoforms which are widely expressed. While the middle nine exons (7 to 15) can be alternatively spliced and located between exons 1-5 and 16-20, which encode CD44 variant (CD44v) isoforms that is revealed presenting under specific pathological progress (Naor et al. 2002). CD44 consists of three major regions: ectodomain (containing the N-terminal region and the membrane proximal area), transmembrane domain, intracellular region (with capacity of signaling regulation), and the diversity of CD44v is found near the membrane proximal region (Idzerda et al. 1989; Screaton et al. 1993). Processing like N-glycosylation, O-glycosylation, addition of heparin sulfate or chondroitin sulfate enables CD44 protein more complex (Greenfield et al. 1999). Specific expression of CD44v has been identified in various cancer cells and tumor samples; accordingly, CD44v could be a useful biomarker for surveying the course of disease (Jiang et al. 2014; Li et al. 2014; Wang et al. 2009; Legras et al. 1998; Khaldoyanidi et al. 1996).

3. CD44/hyaluronan in proliferation of CML

CD44 contributes to cell proliferation in papillary thyroid carcinoma (Kawai et al. 2019). In CML, CD44 is also associated with cell survival (Wang et al. 2017; Chang et al. 2013). In researching the function of arsenic trioxide (ATO) on CML since ATO could decline the expression of BCR-ABL protein and induce the apoptosis of CML (Wang et al. 2017; Zhu et al. 2012), it was found that ATO arrested CML cell line K562 cells in the G0/G1 phase with CD44, β-catenin and cyclinD1 decreased. Another report (Chang et al. 2013) demonstrated the mechanism based on which CD44 affects the proliferation of CML cell. CD44 expression was increased in several types of leukemia patients including CML. CD44 knockdown resulted in proliferation decreased, cell cycle arrest at G0/G1 phase with p21 and cyclin D1changes, and the instability of Wnt/β-catenin pathway in K562 cells and the nude mouse transplantation model. So decreasing CD44 may induce a cell cycle arrest through Wnt/β-catenin pathway.

Acting as a signaling platform binding various ligands, CD44 is the main cellular receptor for hyaluronan (HA), one of the most important glycosaminoglycans of extracellular matrix. HA metabolism and interaction with CD44 play critical roles in oncogenesis and progression of cancers (Karousou et al. 2017; Bourguignon et al. 2008; Bourguignon 2012; Teriete et al. 2004). It is shown that HA synthesized by human CML cell lines is crucial to prevent cells from undergoing senescence and resist the cytostatic effect of vincristine (Lompardía et al. 2013). Imatinib could decrease the HA levels and the surface expression of CD44, however, high molecular weight HA (HMWHA) abrogated the anti-proliferative and pro-senescent effect of imatinib without modifying the imatinib-induced apoptosis (Lompardía et al. 2020). Since the effect of imatinib on CML cell lines could be enhanced by application of HA oligomers (binding HA receptors without acting them) and 4-methylumbelliferone (4MU, inhibitor of HA synthesis), it is suggested that low levels of HA are crucial for an effective therapy with imatinib (Lompardía et al. 2017).

4. CD44 contributes to resistance in CML

It has been assessed that resistance to imatinib occurs in 10-15% and to 2GTKI in <10% of patients in first-line treatment (Hochhaus et al. 2020). Mechanisms being responsible for TKIs resistance can be classified as the BCR-ABL-dependent with BCR-ABL kinase domain mutations being the paramount (Rosenzweig 2018) and the BCR-ABL-independent (Braun et al. 2020; Massimino et al. 2020), including the aberrant activation of the signaling pathways downstream of BCR-ABL1 (Gioia et al. 2011; Packer et al. 2011; Wagle et al. 2016), abnormal expression of influx or efflux transporters (Watkins et al. 2015; Deng et al. 2014), presence of mutations in the epigenetic regulators (Kim et al. 2017), and microenvironmental factors (Traer et al. 2014).

CD44 is revealed to be modulated or play a critical role in BCR-ABL1-independent resistance (Grosso et al. 2009; Zhou et al. 2017; Li et al. 2018). Grosso used the pangenomic microarrays to study the BCR-ABL-independent mode of newly derived imatinib-resistant and PD166326-resistant CML cells which are detected neither with mutations in *BCR-ABL*, nor increased expression of BCR-ABL, MDR1 and Lyn kinase. Several new genes associated with resistance to BCR-ABL inhibitors were identified, and the upregulated CD44, AXL, Fyn and HMGA2 were the especially relevant (Grosso et al. 2009). With analysis on the genome and expression profiles of resistant CML cells, potential benefit of non-BCR-ABL1 targeted therapy combined with or without TKIs are extensively researched, and CD44 seems to be an important molecular involved in (Zhou et al. 2017; Li et al. 2018). A potential benefit of concomitant β-catenin and BCR-ABL inhibition was suggested to prevent or overcome BCR-ABL dependent and independent TKI resistance in BC-CML. An overexpression of β-catenin was observed in BC-CML stem and progenitor cells. Combination of Wnt/β-catenin signaling modulator and nilotinib selectively targeted CML progenitors and inhibited CD44, c-Myc, survivin, p-CRKL and p-STAT5 expression (Zhou et al. 2017). In another landmark research (Li et al. 2018), Li et al. verified that AF1q involved in imatinib resistance via regulating CD44. AF1q was increased and positively regulated CD44 in primary and CD34+ CML cells. Elevated AF1q could promote cell proliferation, antagonize apoptosis and increase engraftment of CML cells in vivo. AF1q occupied the CD44 promoter region, indicating that AF1q was recruited to the CD44 promoter, thus promoting the transcription of CD44. And isoforms of CD44 upregulated by AF1q seems mainly to be CD44 v6 and v10. In addition, blocking CD44 activity by A3D8, a specific CD44 monoclonal antibody, attenuated AF1q-mediated imatinib resistance. These data demonstrated AF1q/CD44 to be a potential target.

5. Role of CD44 in CML LSCs

Conception of LSCs has been proposed since Ph positive clone were unable to be eradicated by intensive chemotherapy (Goto et al. 1982). With the development of flow cytometry, presence of LSCs was confirmed in peripheral blood and bone marrow of patients with chronic-phase CML (Holyoake et al. 1999). LSCs were viable in a quiescent state in the presence of imatinib (Graham et al. 2002) and detectable in the bone marrow of patients even with DMR (Chomel et al. 2011, 2016; Corbin et al. 2011). Accordingly, LSCs are considered to contribute to disease persistence which refers to relapse after TKIs discontinuation, and mechanisms account for persistence are something different from those responsible for resistance (Krause et al. 2007; Bavaro et al. 2019). Identification and comprehension about the features of CML LSCs is a vial field of scientific research in the future, since it is still controversial on the definition of CML LSCs and whether LSCs eradication is necessary to acquire the treatment-free demission (Houshmand et al. 2019). Anyway, to precisely identify and eliminate CML LSCs may improve prognosis of more patients with CML.

CD44 is widely recognized as a cancer stem cell marker in several types of cancers (Xu et al. 2020; Al-Othman et al. 2020; Leng et al. 2018). It has been known since 2006 that CD44 as well as CD13, CD33, is expressed in neoplastic stem cells of various myeloid neoplasms including CML (Florian et al. 2006). Importantly, CD44 is more than a mere stem cell marker (Skandalis et al. 2019; Morath et al. 2016). Inhibiting the expression of CD44 may be beneficial in CML autotransplantation (Krause et al. 2006). BCR-ABL-transduced progenitors from CD44-mutant donors were defective in homing to recipient bone marrow, leading to decreased engraftment and impaired induction of CML-like disease in murine CML, indicating that BCR-ABL positive LSCs depend much on CD44 for homing and engraftment than do normal hematopoietic stem cells (HSCs). Furthermore, the increased expression of CD44 in BCR-ABL positive cells was connected with transcriptional regu-

lation by SCL/TAL1, E-selectin in the vascular niche, engraftment in the BMM, cell cycle progression and response to therapy (Godavarthy et al. 2020). It was implied that SCL/TAL1 is a regulator of the expression of CD44, whereby SCL/TAL1 is activated by AKT downstream of BCR-ABL1. In turn, CD44 influences the cell cycle via its binding to E-selectin since inhibiting the binding of cells to E-selectin in the vascular niche increases cell cycle progression and response to imatinib therapy (Godavarthy et al. 2020). These data suggest that targeting CD44 seems to be an exploitable option in eradication of LSCs in the future.

6. Role of CD44 in CML mesenchymal stem cells (MSCs)

MSCs are not only an important component of the bone marrow, but also the crucial adherent site for HSCs (Miura et al. 2006). CD44, cooperating with other surface markers, contributes to identify the bone MSCs in CML as positive in CD29, CD44, CD105, and negative in CD11b, CD34, CD31, CD45, and HLA-DR (Zhao et al. 2005). In addition to differentiating into different types of cells like osteocyte, adipocyte and neural cells, the CML derived MSCs showed normal karyotype and ultrastructure, without *BCR-ABL* gene expression or tumorigenicity (Zhao et al. 2006).
Depletion of bone marrow MSCs (BM-MSCs) reduced the homing of hematopoietic progenitors to the bone marrow (Méndez-Ferrer et al. 2010). Moreover, failure of BM-MSCs to adhere to hematopoietic cells contributes to CML progression, and mechanism involved is that leukemic cell-derived exosomal miR-711 would be transferred to BM-MSCs and weak the adhesive abilities of BM-MSCs by decreasing the expression of the adhesion molecule CD44 (Jiang et al. 2020). These findings indicated that BM-MSCs from CML patients may have clinical value in the future. In Zhang`s work, co-culture of the BM-MSCs extracted from healthy donors with mononuclear cells extracted from CML patients could secrete a substantial amount of IFN-α to inhibit the proliferation of CML (Zhang et al. 2009). But in another research, co-culture of the BM-MSCs from healthy donors with BC-CML cells induced β-catenin and CD44 expression, which contributed to TKI resistance in BC-CML (Zhou et al. 2017). So the potentiality of MSCs in clinical application needs more knowledge.

7. CD44 and phenotypic shift

Persistence of LSCs or a LSC-like phenotype based on BCR-ABL protein suppression has also been associated with the TKI resistance (Houshmand et al. 2019). Chorzalska et al. reported that long-term exposure to imatinib resulted in enhanced adhesiveness, resistance to imatinib and acquisition of stem cell-like markers (Chorzalska et al. 2017). Those cells exhibited the upregulation of adhesion receptors CD44, VLA-4, CXCR4, pluripotency markers SOX2, SALL4, transcription coactivator YAP, and downregulation of Hippo signaling. It supported the emerging concept of therapy-dependent selection for cells to survival in the chemotherapy by upregulating markers associated with stem cell phenotype and plasticity. Baykal-Köse et al. (2020) also observed a phenotypic shift in imatinib-resistant K562 cells (K562-IR). K562-IR cells proliferated slowly and were highly adherent, with expression of CD45 and other hematopoietic markers decreased indicating that these cells had diverged from their hematopoietic origin. Gene expression profile showed these cells differentially expressed tissue/organ development and differentiation genes. In addition, K562-IR cells were CD34-/CD38-, BCR-ABL-independent and expressed high levels of E-cadherin, caveolin, CD44 but reduced level of β-catenin. It indicated that K562-IR cells did not fully confer with the LSC phenotype.
Growing evidence suggests that epithelial-to-mesenchymal transition (EMT) is highly associated with drug resistance (Du and Shim 2016). EMT is the progress of epithelial cells transforming into cells with a mesenchymal phenotype (Thiery et al. 2009; Chen et al. 2018b). Puissant`s work demonstrated the existence of a small cancer cell population with the potential to exhibit the phenotypic switch responsible for chemoresistance (Puissant 2012). By continuous imatinib exposure, an imatinib-resistant and highly adherent CML cells were selected expressing $CD44^{high}/CD24^{low}$, a property of cancer stem cells, and exhibiting EMT-like phenotype. Overexpression of several EMT markers was also observed in CD34+ CML primary cells from patients poorly responding to imatinib therapy. The $CD44^{high}/CD24^{low}$ imatinib-resistant cells displayed increased adhesion, transmigration and invasion through enhanced αVβ3 integrin expression and signaling that culminate in the activation of the FAK/Akt and ERK1/2 pathways.
It seems that the phenotypic shift was an adaptive process rendering cells under TKI stress to develop the gene phenotype that is suitable for new environmental stresses, and become BCR-ABL independent. Targeted therapy on those special populations is critical for the outcome.

8. Anti-CD44 treatment in CML

Some efforts have been taken to investigate the effect and the possible mechanisms of anti-CD44 monoclonal antibody on normal hemopoietic cells and CML stem/progenitor cells. For example, CD44 was demonstrated to be part of a mechanism by which stromal elements can regulate primitive normal but not leukemic hemopoietic cells (Ghaffari et al. 1997). Three non-cross-reacting anti-human CD44 monoclonal antibodies were identified having significant positive or negative (or no) effects on normal human haemopoiesis in the long-term culture system, however, had no effect on the maintenance of leukemic (Ph+) progenitors from patients with CML.
But in another work, CD44 is indicated of importance in CML leukemic stem/progenitor cells (LSPCs) (Zhang et al. 2010a, b). LSPCs expressing CD34(+), CD38(-) and CD123(+) were isolated from bone marrow cells of patients with newly-diagnosed CML. It was observed that the anti-CD44 monoclonal antibody, IM7, effectively inhibited the adhesion and migration abilities of the LSC *in vitro* (Zhang et al. 2010a), but also induced apoptosis of CML-LSPCs through downregulating c-myc and bcl-2 mRNA expression, and decreasing NF-kappaB activity in CML-LSPCs (Zhang et al. 2010b).
Another important work displayed that overexpression of a CD44 isoform, CD44v3, is characteristic of MBNL3 downregulation-related reversion to an embryonic alternative splicing program of CP-CML progenitors into BC-CML LSCs (Holm et al. 2015). CD44v3 expression promoted stem cell maintenance. Targeting BC-CML LSCs with a human CD44 monoclonal antibody in combination with dasatinib, one of TKIs, impairs LSCs self-renewal. These data provide compelling strategies for selective LSC detection and therapeutic elimination.
It is indicated that in addition to aiming at CD44 isoform protein expression, use of the unique pre-mRNA splicing patterns seen in leukemic cells may facilitate the development of novel splice vector-based therapies (Daines et al. 2013). CD44v6 and CD44v8 were expressed in K562 cells. CD44v6 and CD44v8 splicing constructs fused with GFP or a humanized fragment of Pseudomonas aeruginosa exotoxin A (hPE24) were developed. Transfection of K562 leukemia cells with the GFP-linked splicing constructs led to subsequent production of detectable levels of GFP. Transfection of K562 cells with the hPE24-linked CD44 splice constructs led to significant reduction of cell viability and an increase of apoptosis. Normal human PBMCs were unaffected by following transfection with these constructs.

9. Conclusion

In summary, CD44 emerges as an important molecule of CML cell interacting with the microenvironment, involving in cell survival, resistance and persistence. Nevertheless, some questions remain on the mode of CD44 regulation, since CD44 participates in the regulation of various signaling pathways and being regulated by kinds of molecules. Further extensive investigation should be performed that how CD44 isoforms play distinct roles in development and progression of CML. Focusing on differences between a range of dynamic cell states and developing accurate targeted therapies and drug combinations will have a decisive impact on outcomes.

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