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Integrin Alpha4 as a Therapeutic Target of Acute Lymphoblastic Leukemia

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Acute lymphoblastic leukemia (ALL), characterized by malignancy originated from T- or B- lymphoid progenitors, accounts for 80% of childhood leukemia [1,2]. The incidence of ALL appears a bimodal age pattern and the first peak occurs at ages between 1 and 4 years with a decrease at ages 20 to 59 years, followed by the second peak (modest rise) at ages over 60 years [3]. Though overall cure rates have achieved 85% to 90% in children and 40% to 50% in adults with this disease by current intensive chemotherapy regimens, relapse affects 10~20% of children and ~50% of adults [4-6]. Long-term survival rate for relapsed ALL ranges 30%~35% resulting in the most common death cause in children malignancies, which demands novel therapy modules with effectively targeting drug resistant leukemia clones [5,6].

Bone marrow (BM) microenvironment or hematopoietic stem cell (HSC) niches, which consist of cellular components including osteoblasts, osteoclasts, endothelial cells, mesenchymal stem or stromal cells (MSCs), and extracellular matrix (ECM) [7-9]. Both of osteoblastic and vascular niches are critical for localizing, self-renewal and differentiation of normal HSC and leukemia cells [8,9]. Physically, the marrow microenvironment provides a site for leukemia cells escaping from conventional chemotherapy [10]. These remaining small numbers of leukemia cells, i.e. minimal residual disease (MRD) contribute to relapse of the disease causing failure of treatment [11]. To understand how to effectively eradicate there resistant clone is critical to enhance the cure rate of ALLs.

Integrins, heterodimeric transmembrane glycoproteins consisting of various α and β subunits play important role in adhesion mediated by cell-cell and cell-matrix interaction. In a total, there are 18 different α chains and 8 β subunits in humans, which form at least 24 distinct α/β integrin heterodimers [12]. In addition to function of adhesion, integrins also trigger intracellular signaling pathway such as PI3K/Akt/Bcl2 to regulate the cells in migration, homing, proliferation, differentiation and resistance to apoptosis, thereby contributing to drug resistance of leukemia. Among these 24 integrins, integrin α4 is one of the well-studied molecules over the last decade [13,14]. VLA-4 (Very Late Antigen-4), a noncovalently associated heterodimer of α4 (CD49d) and β1 (CD29) subunits, is a receptor for vascular cell adhesion molecule-1 (VCAM-1/CD106) and fibronectin expressed by MSCs [12]. Integrin α4 (CD49d) or VLA-4 is normally expressed in leukocytes including B- and activated T-lymphocytes. Integrin α4 (α4) has been shown to play a particular important role in interactions between normal HSC or leukemia cells and the BM niches [10,15]. Deletion of α4 integrin gene using interferon-induced conditional knockout adult mice (Mx. creα4flox/flox) resulted in a release of HSCs into circulation, which continued for 50 weeks [16]. Homing to the BM was partially inhibited in parallel to rapid increase uptake by the spleen and early engraftment was impaired in the mice with α4 deletion, indicating the role of α4 in adhesion, migration and survival of HSCs [16].

Mudry et al. showed that the effect of Ara-C– and VP-16–induced cell cycle arrest and apoptosis was diminished by coculture of B-lineage ALL cells with stromal cells, suggesting the supportive role of bone marrow stromal cells in maintaining leukemic cell proliferation and survival during exposure to chemotherapy [17].The protective function of stromal cells from chemotherapy was contributed to adhesion and has been considered as the mechanism of MRD and relapse of ALL [11,17]. The B-cell precursor (BCP) ALL patients at diagnosis of first relapse with higher VLA-4 expression in their BM leukemia cells had significantly worse event-free and overall survival probabilities than those with lowers expression [18]. Interestingly, functionally blocking of VLA-4 using anti- VLA-4 antibody in BCP ALL cell line REH, which expresses high level of VLA-4, decreased the adhesion and the antiapoptotic protein BCL-2, and significantly abolished the cytoprotective effect of stromal cells (L87/4) in response to Ara-C [18].

Recently, Hsieh et al. demonstrated that conditional deletion of α4 enhanced the treatment efficacy of tyrosine kinase inhibitor, nilotinib [19]. Moreover, α4 blockade using Natalizumab, a humanized antibody which has been used clinically to treat the patients with multiple sclerosis and Crohn's disease, deadhered primary human Pre-B ALL cells from stromal cells and sensitized ALL cells toward chemotherapy, proposing α4 inhibition combined with chemotherapy as a novel strategy for pre-B ALL treatment [19,20]. As normal cells also express α4, it would be important to determine the effects of integrin α4 blockade on normal hematopoietic cells. To this end, it has also been shown that α4 blockade using Natalizumab did not affect viability of normal pre-B cells compared to the control IgG4-treated cells as assayed over 48 hours, indicating no short-term toxicity of integrin blockade by Natalizumab on normal pre-B cells [19]. In addition, non-leukemic, immune competent wild type or α4-deficient mice were treated with chemotherapy for 4 weeks and in addition with Natalizumab, and blood counts were monitored to determine toxic effects on normal blood counts [19]. The kinetics of leukocyte and erythrocyte recovery were indistinguishable in the two groups of mice demonstrating that chemotherapy treatment of immunocompetent, α4-deficient mice did not result in excessive hematopoietic toxicity against normal cells. Further toxicity studies including long-term studies of Natalizumab need to be further investigated.

In addition to functional blocking antibody, small molecules have been developed in an attempt to regulate integrin VLA-4 dependent adhesion [21]. Chigaev et al. identified several structurally related

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compounds that were able to reduce binding affinity of VLA-4- specific ligand, and block VLA-4/VCAM-1-dependent cell adhesion [22]. The compounds disrupted the adhesion of the cells in vitro, and mobilized HSC from BM to the peripheral blood, which raises therapeutic possibilities of these small molecules for VLA-4-related malignancies including ALL.

In summary, a role of microenvironment in protecting ALL cells from chemotherapy has been implicated [10,11]. Disruption of the adhesion between ALL cells and the BM stroma has been shown to promote a release of ALL cells from BM to peripheral blood, where chemotherapy might more effectively attack leukemia cells [19]. The exact mechanistic contribution of integrin α4 to drug resistance of leukemia remains to be determined to develop blockade of integrin α4 using either antibody or small molecules for clinical care.

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