(PF455) CD36 AS A POTENTIAL MARKER AND THERAPEUTIC TARGET OF LEUKEMIC STEM CELLS IN ACUTE MYELOID LEUKEMIA

Topic: 03. Acute myeloid leukemia - Biology & translational research

Narges Aghaallaei*[1, 2], Daniel Ivanov[1, 2], Nadine Witzeneder[1, 2], Karin Bauer[1, 2], Katharina Slavnitsch[1, 3], Karoline Gleixner[2], Maik Dahlhoff[3], Peter Bettelheim[4], Wolfgang Sperr[1, 2], Peter Valent[1, 2]

[1]Ludwig Boltzmann Institute for Hematology and Oncology, Vienna, Austria; [2]Medical University of Vienna, Department of Internal Medicine I, Vienna, Austria; [3]University of Veterinary Medicine, Department of Biological Sciences and Pathobiology, Laboratory Animal Medicine, Vienna, Austria; [4]Ordensklinikum Linz, Elisabethinen, Department of Hematology, Linz, Austria;

Background

A major focus of current AML research is the eradication of leukemic stem cells (LSC), a small population of AML cells with *in vivo* leukemia-initiating and sustained self-renewal capacity. AML LSC typically reside in $CD34^+/CD38^-$ and sometimes also in $CD34^+/CD38^+$ subfractions of the malignant clone. While several surface antigens are expressed on LSC, most of these targets are also present on normal hematopoietic stem cells (HSC). Therefore, the identification of more specific LSC-associated markers and targets is critical for the development of curative AML therapies. We identified CD36 as a surface marker expressed in LSC-containing AML subsets. CD36 is a lipid uptake receptor that has been implicated in AML evolution and drug resistance. These observations suggest that CD36 may represent a promising marker and therapeutic target in AML.

Aims

The aims of the present study were to explore expression of CD36 on neoplastic cells in various subsets of AML, to investigate the mechanisms contributing to the expression of CD36 in AML cells, and to examine whether CD36 can be developed as a novel LSC marker and target in AML.

Methods

Surface CD36 expression was analyzed in primary AML cells and AML-derived cell lines (U937, MOLM13, MV4-11, THP-1) by monoclonal antibodies and flow cytometry. The target pathways contributing to CD36 expression were examined by specific signal transduction inhibitors and other anti-neoplastic agents. The engraftment capacity of primary $CD36^+$ AML cells and $CD36^+$ U937 cells and the effects of the CD36-related lipid uptake inhibitor sulfosuccinimidyl oleate (SSO) on *in vivo* engraftment of AML cells was evaluated in NSGS mice.

Results

CD36 was found to be expressed on CD34+/CD38− and CD34+/CD38+ AML cells in various forms of AML, whereas normal HSC did not express CD36. Sorted CD36+ bone marrow (BM) mononuclear cells derived from 4 AML patients also engrafted in NSGS mice, confirming that AML LSC express CD36 (14.4±23.7 percent engraftment of human CD45+ cells). Furthermore, the CD36-related fatty acid uptake inhibitor sulfosuccinimidyl oleate (SSO) was found to induce apoptosis in primary CD34+/CD38− AML LSC (percent of Annexin V/DAPI-positive CD34+/CD38− cells, control [n=8]: 31.6±14%, versus SSO, 100 µM [n=8]: 67.6±21%, $p<0.05$). Correspondingly, purified (sorted) CD36+ U937 cells successfully engrafted NSGS mice, and SSO treatment (1000 µM at 37°C for 1 hour) reduced engraftment compared to untreated controls (controls: 46.2±19.3% [n=13] versus SSO: 29.1±20.5% [n=14]). Moreover, blocking CD36-mediated fatty acid uptake by SSO significantly decreased the growth and survival of U937 cells. Interestingly, vitamin D also suppressed CD36 expression as well as growth in various AML cell lines including U937. We also found that the PI3 kinase blocker BEZ235 and the BRD4-targeting drugs JQ1 and dBET6 counteract CD36 expression in AML cells, indicating that CD36 is regulated by oncogenic signaling pathways.

Summary/Conclusion

CD36 is expressed in LSC-containing BM AML fractions (CD34+/CD38− and CD34+/CD38+) but not in normal HSC. Drugs targeting PI3 kinase or BRD4/MYC and vitamin D suppressed the expression of CD36 in AML cells. The CD36-related fatty acid uptake blocker SSO reduced cell growth/survival in U937 cells and primary AML cells including LSC, and suppressed engraftment of U937 cells in NSGS mice. Whether CD36 can be developed far enough to reach clinical application in AML, remains to be determined.