Human CLPB forms ATP-dependent complexes in the mitochondrial intermembrane space.

Abstract

Human caseinolytic peptidase B protein homolog (CLPB), also known as suppressor of potassium transport defect 3 (SKD3), is a broadly-expressed member of the family of ATPases associated with diverse cellular activities (AAA+). Mutations in the human CLPB gene cause 3-methylglutaconic aciduria type VII. CLPB is upregulated in acute myeloid leukemia (AML), where it contributes to anti-cancer drug resistance. The biological function of CLPB in human cells and mechanistic links to the clinical phenotypes are currently unknown. Herein, subcellular fractionation of human HEK-293 and BT-549 cells showed that a single 57-kDa form of CLPB was present in the mitochondria and not in the cytosolic fraction. Immunofluorescence staining of HEK-293 and BT-549 cells with anti-CLPB antibody co-localized with the mitochondrial staining using a MitoTracker dye. In purified intact mitochondria, CLPB was protected against externally added proteinase K, but it was susceptible to degradation after disruption of the outer membrane, indicating that CLPB resides in the mitochondrial intermembrane space. Overexpressed CLPB, while properly trafficked to the mitochondria, appeared to form large clusters/aggregates that were resistant to extraction with non-ionic detergents and were readily visualized by immunofluorescence microscopy. Importantly, endogenous CLPB formed high molecular weight protein complexes in an ATP-dependent manner that were detected by blue native polyacrylamide gel electrophoresis. These results demonstrate that ATP induces a structural change in CLPB and controls its ability to self-associate or form complexes with other proteins in the intermembrane space of mitochondria.

PMID: 32866687 [PubMed — as supplied by publisher]

Outcome of allogeneic hematopoietic cell transplantation after venetoclax and hypomethylating agent therapy for acute myeloid leukemia.

Abstract

The combination of hypomethylating agents with the selective Bcl-2 inhibitor venetoclax (HMA-VEN) has emerged as a highly active regimen in acute myeloid leukemia (AML) both in the upfront as well as relapsed/refractory (r/r) setting. We report our early experience with a cohort of patients who were able to proceed to allogeneic hematopoietic cell transplantation (alloHCT) after HMA-VEN therapy. Thirty two AML patients (19 r/r and 13 de novo) with a median age of 62 years underwent alloHCT after HMA-VEN therapy. Twenty two (68.8%) were in CR/CRi at time of HCT. With a median follow up of 14.4 months, the 1-year overall survival was 62.5% and disease-free survival was 43.8%. The 1-year non relapse mortality rate was 18.8 % and cumulative incidence of relapse was 37.5 %. Among patients who underwent alloHCT in CR, the 1-year OS was 77.3% and cumulative incidence of NRM was 9.1%. Cumulative incidence of Grade II-IV acute GVHD was 43.8%. We conclude that HCT post HMA-VEN is associated with favorable allogeneic HCT outcomes in newly diagnosed older AML patients as well as those with r/r AML.

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Pharmacological strategies to overcome treatment resistance in acute myeloid leukemia: increasing leukemic drug exposure by targeting the resistance factor SAMHD1 and the toxicity factor Top2β.

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Pharmacological strategies to overcome treatment resistance in acute myeloid leukemia: increasing leukemic drug exposure by targeting the resistance factor SAMHD1 and the toxicity factor Top2β.

Expert Opin Drug Discov. 2020 Aug 31;:1–5
Authors: Herold N
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Comparison of the clinical phenotype and haematological course of siblings with Fanconi anaemia.

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Comparison of the clinical phenotype and haematological course of siblings with Fanconi anaemia.

Br J Haematol. 2020 Aug 31;:
Authors: Jung M, Mehta PA, Jiang CS, Rosti RO, Usleaman G, Correa da Rosa JM, Lach FP, Goodridge E, Auerbach AD, Davies SM, Smogorzewska A, Boulad F

Abstract

Fanconi anaemia (FA) is a genetic disorder due to mutations in any of the 22 FANC genes (FANCA-FANCW) and has high phenotypic variation. Siblings may have similar clinical outcome because they share the same variants; however, such association has not been reported. We present the detailed phenotype and clinical course of 25 sibling sets with FA from two institutions. Haematological progression significantly correlated between siblings, which was confirmed in an additional 55 sibling pairs from the International Fanconi Anemia Registry. Constitutional abnormalities were not concordant, except for a moderate degree of concordance in kidney abnormalities and microcephaly.

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Selective Degradation of GSPT1 by Cereblon Modulators Identified via a Focused Combinatorial Library.

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Selective Degradation of GSPT1 by Cereblon Modulators Identified via a Focused Combinatorial Library.

ACS Chem Biol. 2020 Aug 31;:

Abstract

Cereblon (CRBN) is an E3 ligase adapter protein that can be reprogrammed by imide-class compounds such as thalidomide, lenalidomide, and pomalidomide to induce the degradation of neo-substrate proteins. In order to identify additional small molecule CRBN modulators, we implemented a focused combinatorial library approach where we fused an imide-based CRBN binding pharmacophore to a heterocyclic scaffold which could be further elaborated. We screened the library for CRBN-dependent antiproliferative activity in the multiple myeloma cell line MM1.S and identified five hit compounds. Quantitative chemical proteomics of hit compounds revealed that they induced selective degradation of GSPT1, a translation termination factor that is currently being explored as a therapeutic target for the treatment of acute myeloid leukemia. Molecular docking studies with CRBN and GSPT1 followed by analog synthesis identified a possible hydrogen bond interaction with the central pyrimidine ring as a molecular determinant of hit compounds’ selectivity. This study demonstrates that focused combinatorial library design, phenotypic screening, and chemical proteomics can provide a suitable workflow to efficiently identify novel CRBN modulators.

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Utility of CD36 as a novel addition to the immunophenotypic signature of RAM-phenotype acute myeloid leukemia and study of its clinicopathological characteristics.

Related Articles

Utility of CD36 as a novel addition to the immunophenotypic signature of RAM-phenotype acute myeloid leukemia and study of its clinicopathological characteristics.

Cytometry B Clin Cytom. 2020 Aug 31;:
Abstract

INTRODUCTION: In 2016, Children Oncology Group (COG) described a new high-risk subtype of acute myeloid leukemia (AML) with a distinct immunophenotypic-signature, RAM-phenotype (RAM-AML). Data on clinical and laboratory features of RAM-AML are still limited to COG report only. Herein, we report the clinicopathological characteristics and detailed immunophenotypic features of RAM-AML patients. In COG report, 38% of RAM-AML belonged to acute megakaryoblastic leukemia (AMKL)-subtype. Hence, we further compared the immunophenotypic features RAM-AML with non-RAM-AMKL diagnosed during the same study period.

METHODS: We included RAM-AML and non-RAM AMKL patients diagnosed between January 2017 and December 2019. We studied their morphological, cytochemical, immunophenotyping, cytogenetic, and molecular characteristics. Mean fluorescent intensity (MFI) and expression-pattern of immunophenotypic markers of RAM-AML were compared with non-RAM AMKLs patients.

RESULTS: We identified 11 RAM-AML (1%) and 21 non-RAM AMKL (1.9%) patients in 1102 pediatric-AML patients. Seven of 11 (63.64%) patients belonged to FAB-M7-subtype. CD56, CD117, and CD33 demonstrated overexpression, whereas CD45 and CD38 showed under-expression in RAM-AML patients. CD36 was consistently negative in RAM-AML, whereas moderate-bright positive in non-RAM AMKL patients. (p CONCLUSION: We report the clinicopathological characteristics and the detailed immunophenotypic profile in the world’s second series of RAM-AML patients. We further report a novel finding of CD36-negative expression as an additional parameter to the multidimensional immunophenotypic signature of this entity.

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Donor-derived myelodysplastic syndrome after allogeneic stem cell transplantation in a family with germline GATA2 mutation.

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Donor-derived myelodysplastic syndrome after allogeneic stem cell transplantation in a family with germline GATA2 mutation.


Abstract

Germline GATA2 heterozygous mutations were identified as complex immunodeficiency and hematological syndromes characterized by cytopenia (monocytes, B-cells, NK-cells), susceptibility to mycobacterium, fungus, or Epstein-Barr virus (EBV) infection, and myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML) development. Herein, we report a patient with AML who had a fatal infection after allogeneic hematopoietic stem cell transplantation (HSCT) due to impaired immune reconstitution associated with GATA2 mutation. A 15-year-old man was diagnosed with AML with monosomy 7. His family history was negative for immunodeficiency and hematological disorders. He attained complete remission after HSCT from an HLA-identical sister. Post-HSCT examinations performed 15 months later revealed pancytopenia, especially
monocytopenia and the absence of B and NK cells, resulting in the occurrence of donor-type MDS. Twenty-one months after HSCT, he developed central nervous system aspergillosis and finally died of the disease. Two months later (24 months after PBSCT), the donor was diagnosed with persistent EBV infection accompanied by MDS with multilineage dysplasia. Genetic analysis of GATA2 revealed a novel heterozygous mutation (c.1023_1026dupCGCC) in both siblings. GATA2 mutations were highly prevalent among adolescent MDS/AML patients with monosomy 7. Therefore, the screening of GATA2 mutations in relatives is necessary when performing HSCT from a relative donor.

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18FDG-PET imaging and histopathology in neuroleukemiosis with acute myeloid leukemia.

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18FDG-PET imaging and histopathology in neuroleukemiosis with acute myeloid leukemia.

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Authors: Kiyoki Y, Matsuoka R, Kaneta T, Nishikii H

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