Acute Myeloid Leukemia

Literature Update

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AML1 protein interacts with Influenza A virus neuraminidase and upregulates IFNβ response in infected mammalian cells.

Related Articles

AML1 protein interacts with Influenza A virus neuraminidase and upregulates IFNβ response in infected mammalian cells.

Lett Appl Microbiol. 2020 Jan 28;:

Authors: Gaur P, Kumar P, Sharma A, Lal SK

Abstract

Neuraminidase (NA) is an integral membrane protein of Influenza A virus (IAV) and primarily aids in the release of progeny virions, following the intracellular viral replication cycle. In an attempt to discover new functions of NA, we conducted a classical yeast two-hybrid screen and found acute myeloid leukemia marker 1 (AML1) as a novel interacting partner of IAV-NA. The interaction was further validated by co-immunoprecipitation in IAV infected cells and in an in-vitro coupled-transcription translation system. Interestingly, we found an increase in the expression of AML1 upon IAV infection in a dose dependent manner. As expected, we also observed an increase in the IFNβ levels, the first line of defense against viral infections. Subsequently, when AML1 was downregulated using siRNA, the IFNβ levels were found to be remarkably reduced. Our study also shows that AML1 is induced upon IAV infection and results in the induction of IFNβ. Thus, AML1 is proposed to be an important player in IFN induction and has a role in an anti-viral response against influenza A virus infection.

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Cellular and molecular architecture of hematopoietic stem cells and progenitors in genetic models of bone marrow failure.

Related Articles

Cellular and molecular architecture of hematopoietic stem cells and progenitors in genetic models of bone marrow failure.

JCI Insight. 2020 Jan 28;:


Abstract

Inherited bone marrow failure syndromes (IBMFSs) such as Fanconi Anemia (FA) and Shwachman-Diamond syndrome (SDS) feature progressive cytopenia and a risk of acute myeloid leukemia (AML). Using deep phenotypic analysis of early progenitors in FA/SDS bone marrow samples we revealed selective survival of progenitors that phenotypically resembled granulocyte-monocyte progenitors (GMP). Whole exome and targeted sequencing of GMP-like cells in leukemia-free patients revealed a higher mutation load than in healthy controls and molecular changes that are characteristic of AML: increased G>A/C>T variants, decreased A>G/T>C variants, increased trinucleotide mutations at Xp(C>T)pT and decreased mutation rates at Xp(C>T)pG sites compared to other Xp(C>T)pX sites and enrichment for Cancer signature 1 (X indicates any nucleotide). Potential pre-leukemic targets in the GMP-like cells from FA/SDS patients included SYNE1, DST, HUWE1, LRP2, NOTCH2 and TP53. Serial analysis of GMPs from a SDS patient, who progressed to leukemia revealed a gradual increase in mutational burden, enrichment of G>A/C>T signature and emergence of new clones. Interestingly, the molecular signature of marrow cells from two FA/SDS patients with leukemia was similar to that of FA/SDS patients without transformation. The predicted founding clones in SDS-AML harbored mutations in several genes including TP53, while in FA-AML the mutated genes included ARID1B and SFPQ. We described an architectural change in the hematopoietic hierarchy of FA/SDS with remarkable preservation of GMP-like populations harboring unique mutation signatures. GMP-like cells might represent a cellular reservoir for clonal evolution.

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Positive expression of PAX7 indicates poor prognosis of pediatric and adolescent AML patients.

Related Articles
Positive expression of PAX7 indicates poor prognosis of pediatric and adolescent AML patients.
Expert Rev Hematol. 2020 Jan 28;1–9
Authors: Yan T, Naren D, Gong Y
Abstract
Objective: Therapeutic advances based on risk stratification and implementation of excellent supportive care measures have significantly improved outcomes for childhood acute myeloid leukemia (AML) over the past 30 years. However, approximately half of all childhood AML cases relapse. Therefore, precise risk stratification is needed for predicting relapse potential.

Methods: RNA-seq data of TARGET-AML and corresponding clinical information of pediatric and adolescent AML cases were downloaded from The Cancer Genome Atlas. Clinical information of 156 patients with gene expression data was extracted. The effects of PAX7 expression profiles on overall survival (OS) and event-free survival (EFS) were analyzed.

Results: Positive expression of PAX7 indicated shorter OS and EFS, especially in patients older than 14 years. Furthermore, positive PAX7 expression also predicted shorter OS and EFS in intermediate- and low-risk group patients, compared to patients with negative PAX7 expression. In addition, patients who have received allogeneic hematopoietic stem cell transplantation (allo-HSCT) in the first complete remission had better outcome than those who did not receive HSCT.

Conclusions: Positive PAX7 expression in pediatric and adolescent AML patients indicates a poor outcome. Hence, the detection of PAX7 expression profiles is helpful for further stratification of intermediate- and low-risk groups.

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Clonal selection in therapy related myelodysplastic syndromes and acute myeloid leukemia under azacitidine treatment.

Related Articles
Clonal selection in therapy related myelodysplastic syndromes and acute myeloid leukemia under azacitidine treatment.
Eur J Haematol. 2020 Jan 28;:

Abstract
INTRODUCTION: Therapy related myelodysplastic syndrome and acute myeloid leukemia (t-MDS/AML) are defined as complications of previous cytotoxic therapy. Azacitidine (AZA), a hypomethylating agent, has showed activity in t-MDS/AML.

OBJECTIVES: We evaluated the clonal dynamics of AZA treated t-MDS/AML.

METHODS: We collected bone marrow samples, at diagnosis and during treatment, from AZA-treated t-MDS/AML patients. NGS on 19 myeloid genes was performed and candidate mutations with a variant allele frequency >5 % were selected.

RESULTS: 7 t-AML and 12 t-MDS were included with median age of 71 (56–82) years old, median number of AZA cycles of 6 (1–15) and median overall survival (OS) of 14 (3–29) months. We observed correlation between AZA response and clonal selection. Decrease of TP53 mutated clone was correlated with response to AZA, confirming AZA efficacy in this subgroup. In some patients, emergence of mutations was correlated with progression or relapse without impact on OS. Clones with mutations in genes for DNA methylation regulation frequently occurred with other mutations and remained stable during AZA treatment, independent of AZA response.

CONCLUSION: We confirmed the molecular complexity of t-MNs and that the follow-up of clonal selection during AZA treatment could be useful to define treatment combination.

PMID: 31990086 [PubMed — as supplied by publisher]

Cell Death Pathways in Lymphoid Malignancies.

Related Articles
Cell Death Pathways in Lymphoid Malignancies.
Authors: Fletcher L, Nahrinsky E, Liu T, Danilov A
Abstract
PURPOSE OF REVIEW: This review highlights the importance of the Bcl-2 family members in lymphoma cell survival and discusses the approaches to modulate their function, directly or indirectly, to advance lymphoma therapeutics.

RECENT FINDINGS: The balance of cell death versus survival is ultimately leveraged at the mitochondria. Mitochondrial outer membrane permeabilization (MOMP) is the critical event that governs the release of pro-apoptotic molecules from the intermembrane mitochondrial space. MOMP is achieved through the coordinated actions of pro- and anti-apoptotic Bcl-2 family member proteins. Recognition of functional alterations among the Bcl-2 family member proteins led to identification of tractable targets to combat hematologic malignancies. A new class of drugs, termed BH3 mimetics, was introduced in the clinic. Venetoclax, a Bcl-2 inhibitor, received regulatory approvals in therapy of chronic lymphocytic leukemia and acute myeloid leukemia. Alternative pro-survival Bcl-2 family proteins, in particular Mcl-1, have been successfully targeted in preclinical studies using novel-specific BH3 mimetics. Finally, anti-apoptotic Bcl-2 family members may be targeted indirectly, via interference with the pro-survival signaling pathways, e.g., phosphoinositide-3 kinase, B-cell receptor signaling, and NF-κB.
Impact of clinical features, cytogenetics, genetic mutations, and methylation dynamics of CDKN2B and DLC-1 promoters on treatment response to azacitidine.

Related Articles
Impact of clinical features, cytogenetics, genetic mutations, and methylation dynamics of CDKN2B and DLC-1 promoters on treatment response to azacitidine.

Ann Hematol. 2020 Jan 28;

Abstract
Azacitidine (AZA) is a DNA hypomethylation agent administered in myeloid neoplasms; however, there is still a lack of established predictors of response. We studied 113 patients with myelodysplastic syndromes (n = 85) or acute myeloid leukemia (n = 28) who received AZA to assess the predictive value on response of clinical features, cytogenetics, and molecular markers. Overall, 46 patients (41%) responded to AZA. Platelet doubling after the first AZA cycle was associated with a better response (68% vs. 32% responders, P = 0.041). Co-occurrence of chromosome 7 abnormalities and 17p deletion was associated with a worse response (P = 0.039). Pre-treatment genetic mutations were detected in 98 patients (87%) and methylation of CDKN2B and DLC-1 promoters were detected in 50 (44%) and 37 patients (33%), respectively. Patients with SF3B1 mutations showed a better response to AZA (68% vs. 35% responders, P = 0.008). In contrast, subjects with mutations in transcription factors (RUNX1, SETBP1, NPM1) showed a worse response (20% vs. 47% responders, P = 0.014). DLC-1 methylation pre-treatment was associated with poor clinical features and its reduction post-treatment resulted in a better response to AZA in MDS patients (P = 0.037). In conclusion, we have identified several predictors of response to AZA that could help select the best candidates for this treatment.

PMID: 31989308 [PubMed — in process]

Prognostic role of SCAMP family in acute myeloid leukemia.

Related Articles
Prognostic role of SCAMP family in acute myeloid leukemia.

Pharmacogenomics J. 2020 Jan 28;

Abstract
Acute myeloid leukemia (AML) is a malignant disease of myeloid hematopoietic stem or progenitor cells characterized by abnormal proliferation of primary and immature myeloid cells in bone marrow and peripheral blood. Gene mutation and expression profiles can be used as prognosis predictors for different prognostic subgroups. Secretory carrier-associated membrane proteins (SCAMPs) are a multigenic family with five members and act as cell surface vectors in the post-Golgi recycling pathways in mammals. Nevertheless, the prognostic and clinical influence of SCAMP family has hardly ever been illustrated in AML. In our study, expression patterns of SCAMP family (SCAMP1-5) were analyzed in 155 AML patients which were extracted from the Cancer Genome Atlas database. In chemotherapy, only subgroup, higher SCAMP1 level was significantly associated with longer EFS and OS (all P = 0.002), and SCAMP1 was confirmed to be an independent favorable factor in un-transplanted patients by Multivariate analysis (all P

PMID: 31988488 [PubMed — as supplied by publisher]

Low-frequency TP53 hotspot mutation contributes to chemoresistance through clonal expansion in acute myeloid leukemia.

Related Articles
Low-frequency TP53 hotspot mutation contributes to chemoresistance through clonal expansion in acute myeloid leukemia.

Leukemia. 2020 Jan 27;
Authors: Yan B, Chen Q, Xu J, Li W, Xu B, Qiu Y

Abstract
TP53 mutations (TP53mut) in AML patients associate with poor prognosis that may affect therapy and outcome. In addition to TP53 mut patients, TCGA AML patient sequencing data show that there are around 3% of patients have detectable low-frequency TP53mut reads. Importantly, these patients showed worse outcome as compared with the TP53 wild type (TP53wt) patients. We have studied the effect of low-frequency TP53mut in two AML cell lines, OCI-AML2 and MV4-11. Both cells have low-frequency
single hotspot TP53mut. Interestingly, the resistant cells derived from both lines have homogeneous TP53mut. TP53mut clones isolated from the parental cells also show increased chemoresistance potential and have higher population of leukemia stem cell (LSC) maker positive cells, a characteristic of chemoresistant cells. When mixed with TP53wt cells, the TP53mut cells show survival advantage suggesting its potential to develop chemoresistance. We previously showed that histone deacetylase inhibitor Romidepsin can re-sensitize chemoresistant cells by eradicating LSC marker positive cells. Here we further show that Romidepsin can reactivate p53 targeted genes which are dysregulated in TP53mut cells and preferentially targets TP53mut subpopulation. Therefore, our study shows that low-frequency TP53mut is linked to chemoresistance and sheds light on therapeutic strategies for treatments on chemoresistance.

PMID: 31988438 [PubMed — as supplied by publisher]

Whole-genome fingerprint of the DNA methylome during chemically induced differentiation of the human AML cell line HL-60/S4.

Related Articles

Whole-genome fingerprint of the DNA methylome during chemically induced differentiation of the human AML cell line HL-60/S4.

Biol Open. 2020 Jan 27;


Abstract

Epigenomic regulation plays a vital role in cell differentiation. The leukemic HL-60/S4 promyelocytic cell can be easily differentiated from its undifferentiated promyelocyte state into neutrophil- and macrophage-like cell states. In this study, we present the underlying genome and epigenome architecture of HL-60/S4 through its differentiation. We performed whole genome bisulphite sequencing of HL-60/S4 cells and their differentiated counterparts. With the support of karyotyping, we show that HL-60/S4 maintains a stable genome throughout differentiation. Analysis of differential CpG methylation reveals that most methylation changes occur in the macrophage-like state. Differential methylation of promoters was associated with immune related terms. Key immune genes, CEBPA, GFI1, MAFB and GATA1 showed differential expression and methylation. However, we observed strongest enrichment of methylation changes in enhancers and CTCF binding sites, implying that methylation plays a major role in large scale transcriptional reprogramming and chromatin reorganisation during differentiation. Correlation of differential expression and distal methylation with support from chromatin capture experiments allowed us to identify putative proximal and long-range enhancers for a number of immune cell differentiation genes, including CEBPA and CCNF. Integrating expression data, we present a model of HL-60/S4 differentiation in relation to the wider scope of myeloid differentiation.

PMID: 31988093 [PubMed — as supplied by publisher]

Body size and obesity during adulthood, and risk of lympho-haematopoietic cancers: an update of the WCRF-AICR systematic review of published prospective studies.

Ann Oncol. 2019 Apr;30(4):528-541

Authors: Abar L, Sobiecki JG, Cariolou M, Nanu N, Vieira AR, Stevens C, Aune D, Greenwood DC, Chan DSM, Norat T

Abstract

BACKGROUND: To summarise the evidence on the associations between body mass index (BMI) and BMI in early adulthood, height, waist circumference (WC) and waist-to-hip ratio (WHR), and risk of lympho-haematopoietic cancers.

METHOD: We conducted a meta-analysis of prospective studies and identified relevant studies published up to December 2017 by searching PubMed. A random-effects model was used to calculate dose-response summary relative risks (RRs).

RESULTS: Our findings showed BMI, and BMI in early adulthood (aged 18-21 years) is associated with the risk of Hodgkin’s and non-Hodgkin’s lymphoma (HL and NHL), diffuse large beta-cell lymphoma (DLBCL), Leukaemia including acute and chronic myeloid lymphoma (AML and CML), and chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM). The summary RR per 5kg/m2 increase in BMI were 1.12 [95% confidence interval (CI): 1.05–1.20] for HL, 1.05 (95% CI: 1.03–1.08) for NHL, 1.11 (95% CI: 1.05–1.16) for DLBCL, 1.06 (95% CI: 1.03–1.09) for ML, 1.09 (95% CI: 1.03–1.15) for leukaemia, 1.13 (95% CI: 1.04–1.24) for AML, 1.13 (95% CI: 1.05–1.22) for CML and 1.04 (95% CI: 1.00–1.09) for CLL, and were 1.12 (95% CI: 1.05–1.19) for NHL, 1.22 (95% CI: 1.09–1.37) for DLBCL, and 1.19 (95% CI: 1.03–1.38) for FL for BMI in early adulthood analysis. Results on mortality showed a 15%, 16% and 17% increased risk of NHL, MM and leukaemia, respectively. Greater height increased the risk of NHL by 7%, DLBCL by 10%, FL by 9%, MM by 5% and Leukaemia by 7%. WHR was associated with increased risk of DLBCL by 12%. No association was found between higher WC and risk of MM.

CONCLUSION: Our results revealed that general adiposity in adulthood and early adulthood, and greater height may increase the risk of almost all types of lympho-haematopoietic cancers and this adds to a growing body of evidence linking body fatness to several types of cancers.

PMID: 31987269 [PubMed — in process]
Preserving fertility in female patients with hematological malignancies: a multidisciplinary oncofertility approach.

Related Articles
Preserving fertility in female patients with hematological malignancies: a multidisciplinary oncofertility approach.
Authors: Salama M, Anazodo A, Woodruff TK

Abstract
Oncofertility is a new interdisciplinary field at the intersection of oncology and reproductive medicine that expands fertility options for young cancer patients. The most common forms of hematological malignancies that occur in girls and young women and therefore necessitate oncofertility care are acute lymphocytic leukemia, acute myeloid leukemia, non-Hodgkin’s lymphoma, and Hodgkin’s lymphoma. Aggressive gonadotoxic anticancer regimens including alkylating chemotherapy and total body irradiation are used often in treating girls and young women with hematological malignancies. The risks of gonadotoxicity and subsequent iatrogenic premature ovarian insufficiency and fertility loss depend mainly on the type and stage of the disease, dose of anticancer therapy as well as the age of the patient at the beginning of treatment. To avoid or at least mitigate the devastating complications of anticancer therapy-induced gonadotoxicity, effective and comprehensive strategies that integrate different options for preserving and restoring fertility ranging from established to experimental strategies should be offered before, during, and after chemotherapy or radiotherapy. A multidisciplinary approach that involves strong coordination and collaboration between hematono-cologists, gynecologists, reproductive biologists, research scientists, and patient navigators is essential to guarantee high standard of care.

PMID: 31984320 [PubMed]

Patient similarity by joint matrix trifactorization to identify subgroups in acute myeloid leukemia.

Related Articles
Patient similarity by joint matrix trifactorization to identify subgroups in acute myeloid leukemia.
JAMIA Open. 2018 Jul;1(1):75–86
Authors: Vitali F, Marini S, Pala D, Demartini A, Montoli S, Zambelli A, Bellazzi R

Abstract
Objective: Computing patients’ similarity is of great interest in precision oncology since it supports clustering and subgroup identification, eventually leading to tailored therapies. The availability of large amounts of biomedical data, characterized by large feature sets and sparse content, motivates the development of new methods to compute patient similarities able to fuse heterogeneous data sources with the available knowledge.

Materials and Methods: In this work, we developed a data integration approach based on matrix trifactorization to compute patient similarities by integrating several sources of data and knowledge. We assess the accuracy of the proposed method: (1) on several synthetic data sets which similarity structures are affected by increasing levels of noise and data sparsity, and (2) on a real data set coming from an acute myeloid leukemia (AML) study. The results obtained are finally compared with the ones of traditional similarity calculation methods.

Results: In the analysis of the synthetic data set, where the ground truth is known, we measured the capability of reconstructing the correct clusters, while in the AML study we evaluated the Kaplan-Meier curves obtained with the different clusters and measured their statistical difference by means of the log-rank test. In presence of noise and sparse data, our data integration method outperform other techniques, both in the synthetic and in the AML data.

Discussion: In case of multiple heterogeneous data sources, a matrix trifactorization technique can successfully fuse all the information in a joint model. We demonstrated how this approach can be efficiently applied to discover meaningful patient similarities and therefore may be considered a reliable data driven strategy for the definition of new research hypothesis for precision oncology.

Conclusion: The better performance of the proposed approach presents an advantage over previous methods to provide accurate patient similarities supporting precision medicine.

PMID: 26389432