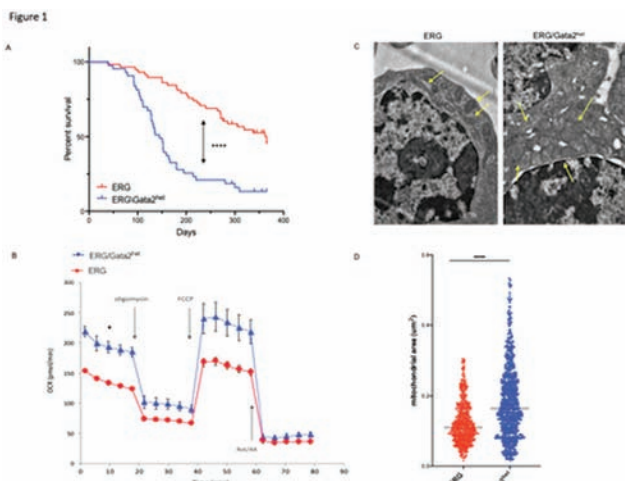


a higher mitochondrial content. Strikingly, imaging by Transmission Electron Microscopy revealed a prominent disruption of ERG/Gata2^{mut} mitochondria, characterized by swollenness and abnormal ill-defined cristae. Significantly, similar metabolic signature was detected in RNA expression profiles of Inv(3)/GATA2^{mut} AML patients, compared with Inv(3)/GATA2^{wt}, and similar mitochondrial aberrations were observed in CD34+ bone marrow cells of GATA2^{+/R396W} pediatric patient.



Summary/Conclusion: We created a mouse model displaying GATA2 tumor-suppressive role. Gata2 haploinsufficiency prime hematopoietic cell for oncogenic transformation. The preleukemic phenotype is characterized by increased proliferation, oxidative phosphorylation, and disrupted mitochondria. Similar patterns were found in human. Abnormally enhanced mitochondrial activity occurs early upon exposure of GATA2 haploinsufficient hematopoietic cells to a myeloid leukemia oncogene and could be potentially targeted to prevent leukemia development.

AML cell biology

S130 NOVEL INSIGHTS INTO GENOMIC CLASSIFICATION AND PROGNOSIS IN ACUTE MYELOID LEUKEMIA BASED ON A PAN-EUROPEAN PUBLIC-PRIVATE PARTNERSHIP, THE HARMONY ALLIANCE

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Background: Given the molecular heterogeneity underlying hematologic malignancies (HMs), large cohorts need to be analyzed to capture how genetic aberrations can affect treatment outcome. Within the HARMONY Alliance, we have built a large "Big Data for Better Outcome" platform for HMs with the aim to put together ~100000 cases of AML, ALL, CLL, MM, MDS, NHL, and pediatric HMs.

Aims: We report first results of our "proof-of-principle" AML study based on the first ~5000 AML cases.

Methods: Following the implementation of a *de facto* anonymization and a data harmonization process using the Observational Medical Outcomes Partnership (OMOP) common data model, we have implemented gene-gene interaction analyses for co-occurrence and mutual exclusivity, a hierarchical Dirichlet process for class discovery, and a Bradley-Terry analysis to estimate clonal evolution. To assess the effects of genomic and clinical data on rates of remission, relapse and survival, we have fitted prognostic multistage models.

Results: To date the platform comprises n = 4986 AML data sets, and first analyses were based on n = 2941 patients (pts) with combined clinical and molecular information available. Male to female ratio was 53% vs. 47%, and the median age was 52.4 (18.0–91.4) years. The ELN 2017 risk groups were well represented (favorable: n = 808, intermediate: n = 1193, adverse: n = 940), and n = 1251 pts were treated with an allogeneic stem cell transplantation (alloSCT), whereas n = 1690 pts received conventional consolidation. Gene-gene interaction analysis confirmed known patterns of co-occurrence and mutual exclusivity, and provided e.g. additional evidence for the co-occurrence of *EZH2* mutations with *RUNX1* and *STAG2* mutations. Similarly, cluster analysis allowed the subdivision of "unique" ELN risk groups. For example, analysis of our large data set showed two inv(16) predominated subclasses that differed in outcome. One was mainly characterized by *NRAS* mutations, whereas the other one showed *KRAS*, *KIT*, *FLT3-ITD* and *CBL* mutations. Based on the Bradley-Terry analysis of the variant allele frequency (VAF), we could further refine the model of clonal evolution. Our large data set does more clearly demonstrate that epigenetic driver mutations in genes affecting DNA methylation (e.g. *DNMT3A*, *TET2*, *IDH1/2*) are very early events, while mutations in histone modifying enzymes (e.g. *KMT2D*, *EZH2*, *ASXL1*, *EP300*) occur later. Finally, first outcome analyses could confirm the predictive power of mutations with regard to overall survival (OS) following an alloSCT. HARMONY results confirmed that for many high-risk genotypes such as e.g. *TP53* mutation patients do only benefit little from an alloSCT (median OS of 90 days without alloSCT vs. 382 days following alloSCT, p < 0.001). However, other higher risk genotypes such as *DNMT3A* in combination with *PTPN11* mutations can have a much larger survival benefit from an alloSCT (median OS 427 days without alloSCT vs. 1493 days following alloSCT, p = 0.027).

Summary/Conclusion: First results prove the benefit in combining European data sets in the HARMONY Alliance platform and demonstrate that OMOP harmonized big data sets will allow us to individualize patient management and to significantly improve outcomes. As the collection of HMs and the analysis of the data is an ongoing effort, by the time of the EHA Annual Meeting in Frankfurt we will show data of >7000 AML cases including a validation data set comprising an additional ~3000 AML cases with molecular data available that are currently submitted to the HARMONY platform (*HD and GO contributed equally to the work).

S131 THE NATURAL HISTORY AND FITNESS LANDSCAPE OF CLONAL HEMATOPOIESIS

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