Poster 13: Methylome-based clustering of mutant IDH1 acute myeloid leukemia reveals robust clusters associated with response to targeted therapy

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Background: Mutations in the genes isocitrate dehydrogenase 1 and 2 (IDHJ, IDH2) occur in 6 to 20% of patients with acute myeloid leukemia (AML) respectively. Mutant IDH acquire a neomorphic activity, producing an oncometabolite, (D)-2-hydroxyglutarate (D-2HG) which competitively inhibits a-ketoglutarate-dependent enzymes, such as the ten-eleven translocation (TET) family of DNA hydroxylases and some histone demethylases. As a result, IDH-mutant AML exhibit a hypermethylated CpG phenotype and increased histone methylation, leading to an aberrant gene expression profile and differentiation arrest. Allosteric inhibitors to IDH-mutant proteins (e.g., ivosidenib for IDHI and enasidenib for IDH2) suppress D-2HG production and demonstrate an -40% overall response rate in patients with IDH mutant relapsed and refractory (R/R) AML. Clinical response to IDH inhibitors (IDHi) can be durable, but primary and secondary resistance to single-agent therapies remain major clinical challenges. Recently, evidence accumulated that gene mutations and gene expression profiles are associated with clinical resistance to IDHi.

Objective and method: In this work, we analyzed DNA methylation at baseline IDH mutant AML samples to search for robust subgroups. Learning methylation profiles were obtained from IDH mutant AML samples referenced in public data bases, TCGA and OHSU, and data deposited to the GEO repository (GSE153349). Subtypes were defined by consensus clustering of the 20, 15, 10, 5 and 1% most variable probes. When available, RNA expression links with methylation-based subgroups and methylation levels were also explored.

Results: Unsupervised clustering ofDNA methylation delineates 5 DNA methylation subtypes (Al, A2, B, Cl, C2), characterized by distinct CpG island methylator phenotype (G-CIMP) and co-associated mutations. Al and A2 subtypes showed a "hypomethylated" state and a dysregulation of major histocompatibility complex (MHC)-associated genes, both at the methylation and the expression level. Notably the Al subtype was the sole subtype significantly associated with response to IDHi: all CR patients belong to this subtype. The B subtype was exclusively composed of IDH2 mutant AML and harbors a CIMP-like phenotype. Altered oxidative phosphorylation (OXPHOS) and mitochondrial fonctions characterized the C 1 and C2 subtypes. These results show that distinct methylation profiles exist within AML with an IDH mutation, impacting the response to targeted therapy.