**POSTER 28: CMML patients with low expression of TP53 point to AML transformation**

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**Background and aims**: The tumor suppressor gene TP53 is commonly mutated in cancers, but TP53 mutations are rare (<1%) in chronic myelomonocytic leukemia (CMML) cells.

**Methods:**We used targeted gene sequencing with bulk RNA sequencing of enriched monocytes, immunofluorescence analysis of P53 protein in CMML monocytes compared to age-matched controls and single cell analysis of CD14+ and CD34+ cells in CMML. CD14, CD16 and CD300E expression by flow cytometry was studied in patients and elderly controls.

**Results:** In a series of 129 CMML patients, we detected a heterogeneous expression of TP53 with patients expressing low level. Using the two extreme groups, this decreased expression of TP53 correlated with an increased risk of AML transformation. Confirming these results, immunofluorescence analysis of P53 protein demonstrates TP53 low expression in 28% of CMML patients. scRNAseq analysis of 4,759 cells identified the accumulation of LMPP and immature monocytes in patients with low level of p53 expression. Immature monocytes were characterized by low expression of CSF1R, EGR1 (by RT-qPCR, IF, scRNAseq), KLF4 and IRF8 (scRNAseq) in patients expressing weakly TP53.

Looking for the mechanisms involved in TP53 down-regulation, we identified a correlation between TP53 and EGR1 (Early growth response protein 1) in CMML cells. EGR1 transcription factor is localized on TP53 promoter in cord blood cells undergoing monocytic differentiation. siRNA-mediated decrease in EGR1 expression decreases also TP53 expression in human CMML primary monocytes. EGR1 also regulates the expression of CSF1R gene, which encodes the receptor for M-CSF, and a correlation between TP53 and CSF1R is also observe, confirming that these monocytes may be more immature.

Strengthening this hypothesis, a continuum CD14 monocyte population was observed, one with high level of CD300E, representing mature monocytes, and the other with lower level of CD300E, referring to more immature monocytes whose proportion increased in patients with low level of p53 expression.

**Conclusion:** While TP53 mutations are rare in CMML, its gene expression is decreased in a fraction of patients as consequence of EGR1 down-regulation, which correlates with altered maturation of the monocytic lineage and a poor patient outcome.