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**Gene Regulatory Complexes and Networks regulated by the ERG oncogene**

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ERG is an ETS-family transcription factor implicated in many important biological processes, including the maintenance and regulation of hematopoietic stem and progenitor cells and for lineage development. Aberrantly increased expression of ERG is observed in many cancers including T-acute lymphoblastic leukemia (T-ALL) and acute myeloid leukemia (AML), and is associated with a very poor prognosis in both contexts. Moreover, ERG has been demonstrated to directly transform and to be involved in the proliferation and maintenance of leukemic cells in human T-ALL and AML. However, little is known about the specific mechanisms involved in the transcriptional regulation of individual target genes by ERG, the composition of ERG-containing gene regulatory complexes (GRC) and the direct leukemic mechanisms regulated by ERG.

In most AML cell lines that we studied, *ERG* inactivation leads to a decrease in cell proliferation and an increase in differentiation and cell death, suggesting that ERG, independently of different upstream mutations and varied levels of expression, controls a common, indispensable network that prevents apoptosis and differentiation to maintain leukemias. To identify and understand the common network controlled by ERG, I integrated ChIPseq analysis in 10 AML patients and 6 AML cell lines with RNA-Seq before and after *ERG*-knockdown (KD) in the cell lines. These analyses showed that ~60% of the ERG binding events are shared across all AML patients and cell lines, also suggesting a common regulatory network. The transcriptional changes imposed by the KD of *ERG* validate its role as both an activator and a repressor of

gene expression and >50% of the differential genes demonstrated ERG binding, suggesting direct ERG regulation. However, surprisingly, very few genes were commonly deregulated in the 6 AML cell lines, suggesting cell-type specific gene regulation and ERG networks. The role of ERG to organise 3D genome organisation was demonstrated by Hi-ChIP and specific ERG partners identified, using endogenous immunoprecipitation associated with mass spectrometry in 3 AML cell lines. Of note, both 3D genome organisation and ERG interactants were also cell-type specific, thus explaining the cell-type specific gene regulation.

In conclusion, despite highly conserved chromatin binding and a similar cellular effect after *ERG*-KD, ERG regulates distinct molecular networks via 3D genome organization and specific GRC in a context specific manner.