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Commentary

Deciphering "B-others": Novel fusion genes driving B-cell acute lymphoblastic leukemia

Shai Izraeli

Department of Pediatric Hematology and Oncology, Leukemia Research Section, Edmond and Lily Children's Hospital, Sheba Medical Center, Ramat Gan 52621, Israel
Department of Molecular Human Genetics and Biochemistry, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. While most children with ALL are cured, the prognosis in adolescence and young adults (AYA) as well as older individuals is worse. The deleterious effects of age on prognosis are partially explained by the decrease of the good prognosis initiating chromosomal aberrations (*ETV6-RUNX1* fusions and hyperdiploidy) and an increase of bad prognosis subtypes (*BCR-ABL1* and *MLL* translocations). Yet as most of the genomic studies were done on childhood ALL, relatively little is known on AYA and adult ALL. Especially less is known on the genomic characteristics of the "B-others" subgroup – the heterogeneous subgroup of ALLs lacking the known chromosomal translocations.

The *EBioMedicine* paper by Liu et al. from the Shanghai Institute of Hematology (Liu et al., 2016) markedly fills this void of knowledge. They performed DNA sequencing of close to 400 children and adults diagnostic and remission samples of ALL, identifying 325 recurrent somatic non-synonymous mutations in protein coding genes, a third of which were never reported before. In addition they performed RNA sequencing of 78 adults and 94 children and identified 29 new in-frame fusions. Adult ALLs were characterized with more mutations especially in epigenetic and B cell developmental genes and, as previously reported, by more "B others" ALLs. Yet, reflecting probably the different ethnic origins the frequency of "Philadelphia like" "CRLF2 fusions" ALLs (reviewed in (Izraeli, 2014)) seems to be lower in the Asian patients.

Non-supervised clustering of gene expression divided the ALLs into eight subgroups. It will be interesting to learn if these subgroups overlap with the ones reported by Harvey et al. for an American cohort for pediatric ALLs (Harvey et al., 2010). The most significant findings are the discoveries of in-frame fusions of *MEF2D*, *ZNF384* and *DUX4* genes respectively, each creating a separate subgroup characterized by a distinct gene expression profile. These discoveries are highly complementary to those recently reported by a similar study of ALL in AYA in Japan that has just been published (Yasuda et al., 2016). Single patients with either *MEF2D* or *ZNF384* fusion translocations have been reported before (Prima et al., 2005; Gocho et al., 2015) but these are the first large studies describing the significance of these fusions in pediatric and adult ALLs. Herein I will discuss these three important novel subtypes of ALL in light of the findings by both groups.

Myocyte Enhancer Factor 2D (MEF2D) is a member of a family of transcription factors that participate in neuronal development and myogenesis. The N-terminus of *MEF2D* was fused to one of several partners, most commonly *BCL9*, in about 7% of the patients, mostly adolescents. The immunophenotype and gene expression of *MEF2D* leukemias were very similar to pre-B ALL caused by the *TCF3-PBX1* translocation with high expression of *HDAC9*, a known target of MEF2D. Expression of *MEF2D* fusion in mouse hematopoietic cells arrested B cell differentiation. Although extra caution should be taken on assigning prognostic significance outside a controlled clinical trial, both the Chinese and the Japanese papers noted extremely bad prognosis to the *MEF2D* fusion ALLs suggesting a need for better therapies. It will be interesting to learn if *MEF2D* pre-B ALL will be sensitive to Dasatinib, SYK inhibitors or other drugs targeting the pre-B cell receptor pathway as was recently reported by the Muschen group (Geng et al., 2015).

The second subgroup is characterized by in-frame fusion of one of several genes, most notably *EP300* or *CREBBP*, to *Zinc Finger 384*, detected in 7–12% of the AYA and older patients. *ZNF384* has been shown before to regulate the expression of genes encoding extracellular matrix proteins. Unlike the *MEF2D* fusion leukemias, *ZNF384* fusions characterized very early pro-B ALL, often CD10 negative with expression of myeloid markers and activation of the JAK-STAT pathway. Consistent with these findings ectopic expression of the translocations in mouse hematopoietic progenitors arrested B cell differentiation and caused monoblastic leukemias. However, unlike other Pro-B ALLs, most notably MLL fusion leukemias, it seems from both studies that the prognosis of this ZNF384 fusion ALLs is relatively good.

The third novel discovery is the subgroup of ALL characterized by translocations of the Double Homeobox 4 gene, *DUX4*, into the *IgH* enhancer locus. *DUX4* is located within a *D4Z4* repeat array in the subtelomeric region of chromosome 4q and encodes the transcriptional

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E-mail address: sizraeli@sheba.health.gov.il.

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activator PITX1 (Dixit et al., 2007). Contraction of these repeats is associated with autosomal dominant facioscapulohumeral muscular dystrophy (FSHD). The Tokyo group discovered that the translocation to the *IgH* locus, presented in 10 of 70 AYA patients with ALL, led to high expression of DUX4 with modified C terminus. Significantly, they demonstrated that transduction of mouse pro-B progenitors with *DUX4-IGH* fusion gene caused B cell leukemia in mice. They also discovered the translocation in the B ALL cell line NALM6 and showed that DUX4 was necessary for its growth and survival (Yasuda et al., 2016).

In addition to the newly discovered DUX4 translocation, NALM6 contains a microdeletion in the *ERG* gene (Zhang et al., 2011). Interestingly the Shanghai group discovered that nearly all the DUX4 ALLs had also *ERG* deletions. Microdeletions within the *ERG* gene have been identified in about 5% of childhood ALL. They are characterized with aberrant CD2 expression and despite common presence of IKZF1 deletions they have excellent prognosis. The microdeletions within *ERG* are often associated with aberrant transcripts of ERG that have been suggested to be oncogenic. Yet these aberrant transcripts are not always expressed and ERG deletions are often subclonal and disappear in relapse (Clappier et al., 2014). These mysterious observations have led to the suggestion that "ERG deletions" ALLs may actually be caused by another driving genomic aberration. The findings by Liu et al. that the recently discovered oncogenic *DUX4-IgH* cryptic translocations almost always occur in *ERG* deleted leukemias suggest either that DUX4 is the oncogenic driving event or that DUX4 cooperates with ERG aberrant isoform in the leukemogenesis process.

Together, the two comprehensive genomic studies from China and Japan have greatly enhanced our understanding of ALL in AYA and have identified three novel ALL subgroups with distinct genotype, immunophehnotype and prognostic significance as well as suggestions for potential therapies.

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