Genetic and epigenetic studies offer new therapeutic options for the treatment of T-cell acute lymphoblastic leukemia

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It took many years and an incredible amount of work to determine the draft of the human genome sequence, which was published in 2001.[1] Now, only ten years after the landmark paper describing the first human genome, whole genomes are being sequenced and analyzed at an increasing speed and depth. In a recent study led by Charles Mullighan,[2] twelve genomes of early T-cell precursor acute lymphoblastic leukemia (ETP ALL) have been fully analyzed with the aim of obtaining a better understanding of the unique characteristics of this subgroup of T-ALL which has a high risk of treatment failure.[3] It was previously shown that ETP ALL cases show a characteristic gene expression and immunophenotypic profile with similarities to myeloid cells and hematopoietic stem cells.

T-ALL is typically characterized by the presence of chromosomal aberrations involving the T-cell receptor genes and a variety of transcription factors, thereby deregulating the expression of these transcriptional regulators.[4,5] Most of the T-ALL cases also harbor NOTCH1 or FBXW7 mutations, leading to activation or stabilization of the NOTCH1 pathway. In the past, many chromosomal translocations and mutations have been identified from cytogenetic studies or by candidate gene sequencing approaches. These studies are hampered by the poor quality of karyotyping in many T-ALL cases and are highly biased towards known oncogenes. Recent studies with array comparative genomic hybridization and 4C technologies have further improved our methods for the genome-wide analysis of T-ALL,[5,6] but for mutation analysis these still have limitations. With the possibility of next-generation sequencing, whole-genome sequencing now resolves all these problems, and both chromosomal aberrations and mutations can now be identified in one single experiment. Despite some remaining limitations of the current computational analysis tools, new sequence technologies have already become the standard for DNA and RNA sequence analyses in cancer research.

The study by Zhang and colleagues[2] identified 181 chromosomal rearrangements in the 12 ETP ALL cases that were analyzed by whole-genome sequencing, including novel fusion genes with ETV6, a gene frequently involved in chromosomal translocations. In addition, ETP ALL cases were also characterized by a high frequency of mutations in genes implicated in cytokine or RAS signaling, inactivation of transcriptional regulators with a known role in lymphoid development, and mutation of histone-modifying proteins. It is remarkable to note that many different oncogenic mutations in ETP ALL converge on the JAK/STAT pathway (IL7R mutations, JAK1 and JAK3 mutations), or harbor mutations in NRAS or FLT3, mutations typically found in acute myeloid leukemia. The IL7R mutations are clearly gain-of-function mutations as they transform hematopoietic cells,[2,7] as was also shown in two additional studies.[8,9] These findings pave the way for clinical trials with JAK or FLT3 inhibitors for the treatment of these ETP ALL cases with poor outcome.

A second interesting observation of the study was the identification of frequent mutations in genes encoding epigenetic regulators such as EZH2, SUZ12, EED, SETD2 and EP300.[2] In a separate study by Ntziachristos and colleagues, Loss-of-function mutations and deletions in EZH2 and SUZ12 were identified in 25% of T-ALL, confirming the importance of epigenetic deregulation in this disease.[10] Moreover, this study identified that NOTCH1 activation specifically induces the loss of repressive histone methylation. These findings support the exploration of inhibitors of histone demethylases alone or in combination with NOTCH1 directed therapies for the treatment of T-ALL.

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