Comment on Zhang et al, page 3080

Key pathways as therapeutic targets

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Somatic mutations are important factors in tumorigenesis. In this issue of Blood, Zhang et al have identified recurrent mutations in key signaling pathways in high-risk childhood B-cell precursor acute lymphoblastic leukemia (BCP-ALL) to be exploited in the development of new therapeutic approaches.1

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The treatment of childhood ALL is a success story of the past 40 years, with >85% overall survival at 5 years. Nevertheless, 20% of patients will relapse. As survival after relapse is poor, it is important that those patients at high risk of relapse are identified at the time of diagnosis. Age, white blood cell count, minimal residual disease, and cytogenetics2 are currently the gold standard to determine the risk groups used to stratify pa-

patients for treatment. Authors from this paper by Zhang et al have pioneered the use of genomic technologies to revolutionize our understanding of the genetics of childhood ALL. Their initial study showed that deletions, amplifications, point mutations, and structural rearrangements in those genes encoding the principal regulators of B-lymphocyte development and differentiation were present in ~40% of childhood BCP-ALL. These abnormalities lead to direct disruption of pathways controlling B-cell development and differentiation, thus contributing to BCP-ALL pathogenesis.3 Simultaneously, deletions of other significant genes were identified by others (see figure).3,5 Further, alterations of IKZF1 (which encodes the lymphoid transcription factor IKAROS) were shown to be a marker of poor prognosis in BCP-ALL.6,7 Associations were also found with mutations of JAK2 and overexpression of the cytokine receptor CRLF2, providing potential therapeutic targets.8,9 Authors from this paper by Zhang et al also used gene expression profiling to further resolve the genetic basis of high-risk disease.11 They defined 8 cluster groups (termed ROSE clusters) within which patients shared patterns of gene expression.

Somatic mutations affecting key genes involved in pathways relating to the development of BCP-ALL are known.12 However, for many of these mutations, the clinical and biologic significance, as well as their relationship to one another and other genetic changes, remain unknown. To begin to address these issues, Zhang et al have reported the first large-scale sequence analysis in ALL.1 They sequenced 120 selected candidate cancer genes in a cohort of 187 high-risk patients treated on the Children’s Oncology Group P9906 protocol. The genes were selected on the basis that they were in pathways that were known to be involved in ALL or other cancers, either from genomic studies, expression profiling, or mutational analysis. Such a targeted approach precludes the finding of as yet unknown mutations in BCP-ALL or cancer in general, which might emerge from whole exome sequencing. However, selected coverage of the majority of known significant genes among a well-annotated cohort provides a rational basis on which to build further detailed studies. A total of 179 somatic mutations in 31 genes were identified, 19 of which were recurrently mutated in this patient cohort. However 11 of...
these 19 genes accounted for 81% of all mutations detected. The most frequently mutated genes were NRAS, KRAS, PAX5, and Janus kinases in > 10% of patients each. When these mutations were combined with copy number alterations,7 the following 4 known cancer signaling pathways—B-cell development and differentiation, Ras signaling, JAK/STAT signaling, and the TP53/RBI tumor suppressor—were involved in 68%, 54%, 11%, and 54% of cases, respectively. In a subset of cases, multiple genes from the 4 individual signaling pathways were mutated. More surprising was the finding that the mutations of the Ras signaling pathway were not mutually exclusive; 5 patients had multiple mutations of NRAS or KRAS. These data suggest a strong selection for mutations within these signaling pathways and, as not all genes in these pathways were sequenced, these results likely provide an underestimate of the mutation rates in high-risk B-CP-ALL. With the exception of the B-cell development and differentiation pathways, the frequency of alterations was higher in this high-risk patient cohort than unselected B-CP-ALL patients.9,12 There was a striking difference in frequency of mutations within the 4 major pathways between the ROSE cluster groups. For example, virtually all patients in the R8 subgroup, which is associated with a high incidence of relapse, had mutations in the B-cell development and differentiation pathways. They had a higher frequency of mutations in TP53/RBI and JAK pathways, while the rate of RAS mutations was lower than other subgroups. Notably, each ROSE cluster group was also characterized by distinct patterns of copy number alterations. IKZF1 deletions and rearrangements leading to CRLF2 overexpression were particularly prevalent and significantly associated with cluster group R8. Collectively, these findings indicate that the genetic profile, as defined by the differential gene expression patterns and genomic aberrations, contributes to patient outcome.

In addition to these mutations in key pathways, inactivating mutations were observed in other noncanonical pathways, including ETV6 and CREBBP. Using a similar targeted sequencing approach, authors from this paper by Zhang et al have recently reported the strong association between mutations in the histone acetyltransferase, CREBBP, and relapsed B-CP-ALL.13 These findings endorse the value of comprehensive evaluation of sequence alterations towards yielding additional biologic insights into this disease.

This study has extended the prior knowledge of the genetics of high-risk childhood BCP-ALL. It has begun to decipher the interrelationships between different genetic abnormalities and place them into clinical context. Sequencing of the entire coding genome is likely to add to these findings, while the study of unselected patient cohorts is required to fully establish the clinical relevance. In the meantime, this demonstration that the genetic basis of high-risk BCP-ALL is truly multifactorial has highlighted potential novel therapeautic approaches, for example, targeting of the Ras signaling pathway.

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REFERENCES

Comment on Balusu et al, page 3096

NPM1-mutated AML: targeting by disassembling

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In this issue of Blood, Balusu and colleagues provide preclinical evidences that targeting nucleophosmin (NPM1) induces differentiation and death of acute myeloid leukemia (AML) cells harboring NPM1 mutations.1 These findings establish the rationale for novel treatment strategies in this large subgroup of AML.

NPM1 is one of the most abundant proteins in the nucleolus. Despite its nuclear localization, NPM1 physiologically shuttles constantly across various cell compartments (nucleolus, nucleoplasm, cytoplasm) and this traffic is critical for most of its functions, including regulation of ribosome biogenesis and control of centrosome duplication.1 NPM1 also interacts with the tumor suppressor p14ARF and p53, and influences the cellular apoptotic response, although its exact role in this pathway still remains poorly understood.2 Mutations involving the NPM1 gene are the most frequent molecular alteration in AML with normal karyotype, accounting for ~ 60% of cases (ie, one-third of adult AML).3 As a consequence of these mutations, the NPM1 mutant intracellular traffic is altered leading to its aberrant accumulation in the
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