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Acute myeloid leukemia: something more than a simple molecular defect

Remarkable advances have been made in the past decade in our understanding of the molecular genetic basis of acute myeloid leukemias (AML). Many of our insights have been gained through the cloning and characterization of chromosomal translocation breakpoints, which have identified genes that are causally implicated in disease pathogenesis targeting the transcriptional apparatus in hematopoietic cells either directly or indirectly.[1] There is convincing evidence that gene rearrangements in AML involving transcription factors such as CBF, RARα, the ETS family and the HOX family are necessary for the onset of the disease,[2] but there is also equally compelling evidence that these events are not sufficient to cause a full leukemic phenotype, as evidenced in part by the long latencies required for disease development in the murine models of the disease.[3] These data support the hypothesis that multiple genetic abnormalities rather than a unique molecular defect are necessary for the phenotype of AML. An emerging paradigm is the co-operation between transcription factor fusions and other molecular events such as mutations in the FLT3 and c-kit receptor tyrosine kinases,[4] ras and NF-1 mutations,[5] aberrant activation of the Jak/Stat pathway,[6] epigenetic changes in the promoter regions of tumor suppressor genes[7] and dysregulation of the cytokine network genes in the pathogenesis of AML.[8] In such a model, additional abnormalities confer proliferation and/or anti-apoptotic activity to the hematopoietic cells, while the transcription factor fusion impairs normal differentiation pathways.

This issue of the Haematologica contains two interesting pieces of this still unsolved puzzle. First, Larramendy *et al.*[9] using cDNA microarray analysis show that several genes which are known to be involved in chromosomal translocations and fusions (i.e., FGFRI, MYC, NPM1 and DEC) were differentially expressed in AML. As none of these translocations was observed in their cases, the finding suggests that these genes are also activated by mechanism other than translocations. Second, Bruserud *et al.*[10] in a large series of consecutive AML patients demonstrated that leptin, a regulator of fat metabolism and angiogenesis, enhances spontaneous proliferation and constitutive cytokine release by native AML blasts.

Although the findings reported here may be the result of targeting the same signal transduction and transcriptional pathways by groups of genetically heterogeneous AMLs, the papers also extend our view of the AML as a collaboration between several oncogenic proteins. Many oncoproteins confer a proliferative and/or survival advantage, whereas other proteins impair hematopoietic differentiation. The two together cause the AML phenotype of enhanced proliferation and survival with impaired differentiation.

Much effort must be made to understand the wealth and complexity of these molecular genetic data. We need to identify the downstream effectors that are activated by mutations in leukemia. We need to know more about the genetics of deletions associated with AML, the role of transcriptional silencing induced by promoter hypermethylation, and the role of cytokine disturbances and angiogenesis in AML in order to answer two definitive questions: how does one identify therapeutic strategies that might be effective for a majority of leukemias when there are more than a hundred known molecular alterations and, how do we rationally approach targeted therapy for hematologic malignancies that are the consequence of more than one genetic event – is targeting one mutation adequate?[11]

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Inside Haematologica: clinical follow-up after autologous stem cell transplantation in patients with multiple myeloma

In this issue, Alegre *et al.*[1] report data showing that the patterns of relapse of multiple myeloma after high-dose therapy are very heterogeneous, indicating the need for an individual approach during clinical follow-up after transplantation. The authors also comment that new drugs such as thalidomide may modify the outcome of these patients following transplantation. For a better comprehension, the reader is referred to pertinent papers on this topic that have recently appeared in Haematologica.[2-16]

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