PATHOGENESIS OF CHRONIC MYELOGENOUS LEUKEMIA

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It is generally recognized that chronic myelogenous leukemia (CML) in its chronic phase is induced by a reciprocal translocation between chromosomes 9 and 22, t(9;22) (q34;q11), which generates the Philadelphia (Ph) chromosome and the fusion gene BCR-ABL. The BCR-ABL gene is transcribed into a mRNA[1] and translated into a protein product, the P210bcr/abl protein.[2] Formal demonstration that this gene and its product play a role in the pathogenesis of CML was obtained by showing that mouse bone marrow transfected with an expression vector for the BCR-ABL gene produced a CML-like syndrome when transplanted into syngeneic recipients.[3]

Compared with that of the normal ABL gene, P145abl,[2] the protein product of P210bcr/abl shows greater and intrinsic protein tyrosine kinase (PTK) activity, which is presumably responsible for its transforming potential. By introducing a series of deletions and substitutions in the BCR sequences of the fusion gene, Muller et al.[4] showed that sequences from the first BCR exon specifically activate ABL PTK activity. More recently, Pendergast et al.[5] demonstrated that sequences from the first BCR exon code for amino acids involved in binding with the GRB-2 adaptor protein.

This protein binds tyrosine-phosphorylated sequences in receptor tyrosine kinases. Binding with GRB-2 links receptor PTK, and possibly non-receptor PTK such as P210 bcr/abl, to the ras-signaling pathway, which is involved in the control of cell proliferation. These data suggest that GRB-2 has a role in BCR-ABL-mediated oncogenesis and that ras function may be upregulated by P210bcr/abl. Indeed, upregulation of ras function has been demonstrated in P210bcr/abl transformed myeloid cell lines.[6] In addition, Cicchetti et al.[7] observed that the SH3 domain of the normal ABL gene product,

P145abl, binds to a protein, 3BP-1, which might have GAP (GTPase activating protein) activity. This implies that by means of its SH3 domain normal P145abl might inactivate signaling through the ras system; it would be interesting to know whether P210-bcr/abl is still able to bind 3BP-1 or to trigger its GAP activity.

Several biological mechanisms relating the presence of P210bcr/abl with the CML phenotype have been suggested. As mentioned, P210 bcr/abl could activate the ras signaling system, which is involved in signal transduction from growth factor and cytokine receptors. Several lines of evidence suggest a relationship between P210 bcr/abl and hematopoietic growth factors. This might be in the form of activation of autocrine mechanisms, increased sensitivity to, or independence from hematopoietic growth factors, or reduced sensitivity to growth inhibitors.

First evidence for the involvement of P210 bcr/abl in hematopoietic growth factor signal transduction was provided by the work of Daley and Baltimore.[8] These authors showed that a growth factor-dependent cell line became independent when it expressed a BCR-ABL gene. Apparently there was no autocrine growth factor production by the transformed cells. In this model, however, P210bcr/abl initiates a signal transduction pathway that partially overlaps the one activated by hematopoietic growth factors such as IL-3 and GM-CSF.[9]

A further advance in understanding the biology of BCR-ABL-transformed cells was provided by Gishizky and Witte.[10] These authors showed that mouse bone marrow cells infected with a retrovirus carrying BCR-ABL cDNA acquired growth factor independence as a later event following transformation, suggesting that BCR-ABL activates a multistep process in which

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the phenotype of transformed cells becomes progressively more malignant. Interesting findings have also emerged from long-term bone marrow cultures.[11,12] In this system CML primitive progenitor cells, the so-called long term culture initiating cells or LTC-IC,[13] proliferate continuously without undergoing periodic fluctuation between the G0 and S phases of the cell cycle as their normal counterparts do.[14] So far, the reasons for this difference are not completely understood, since no differences exist between normal and CML cells either in response to hemopoietic growth factors or in production of growth factors by bone marrow stromal cells.[14,15] An alternative explanation might be that reduced responsiveness of CML cells to inhibitors of hematopoiesis could be responsible for their growth advantage with respect to normal LTC-IC. TGF-β and MIP-1α, two well-known inhibitors of hemopoiesis, have been widely investigated;[16,17] although TGF-β had similar effects on both normal and CML LTC-IC, the latter appeared to be unresponsive to MIP-1α.[18] Similar results were obtained using another inhibitor of hematopoiesis, the tetrapeptide AcSDKP. This agent, while keeping normal progenitor cells in the G0 phase of the cell cycle, has no action on CML progenitors.[19] How these effects relate to BCR-ABL function is unclear.

In the present issue of Haematologica a paper by Balleari et al.[20] reports that increased levels of GM-CSF and G-CSF can be detected in the serum of some patients with chronic myelogenous leukemia. The possiblity that this is a consequence of autocrine and/or paracrine mechanisms contributing to the pathogenesis of the disease is appealing,[21] although, as seen above, other investigators have argued against this hypothesis.[8,15] Such disparate observations, however, may not be mutually exclusive. Since terminally differentiated blood cells can synthesize hematopoietic growth factors, one possibility is that enhanced production of growth factors is due to the increased mass of differentiated cells in CML. In this view, initial expansion of the CML clone would be independent of enhanced production of hematopoietic growth factors; this might occur as a later event, when important leukocytosis is already present.

The observation that growth factor levels were not increased in patients treated with interferon-α is also interesting and suggests that suppression of growth factor production by interferon contributes to its therapeutic effect.

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