Chronic Myelogenous Leukemia Progenitors Display a Genetically Unstable Personality
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Chronic myelogenous leukemia (CML) is a hematopoietic stem cell disorder caused by the BCR–ABL tyrosine kinase oncogene, which induces constitutive activation of growth and viability signaling pathways (1). CML cells are dependent on the elevated kinase activity of BCR–ABL, as demonstrated by the high rates of hematologic remissions induced by the ABL kinase inhibitor imatinib mesylate (Gleevec). Although complete hematologic remission rates occur in more than 95% of patients, only a minority enter a molecular remission in which BCR–ABL is undetectable by polymerase chain reaction. In acute phase, characterized by an increase of immature blast cells in the peripheral blood, only about 70% of patients have a clinical response, and most of them relapse within a few months (2). There is a growing amount of data suggesting that CML stem cells are partially resistant to imatinib (3–6). These stem cells are thought to persist for years despite imatinib therapy and ultimately may develop new mutations that lead to relapse or progression. This poses a serious problem, because the most recent review of the International Randomized Interferon versus STI571 clinical trial indicates that about 4% of stable-phase patients in complete hematologic remission will relapse each year (2). In many cases, relapse is due to point mutations in the kinase domain of BCR–ABL that reduce imatinib binding (7). Thus, the apparent resistance of CML stem cells to kinase inhibition represents a considerable obstacle in treating this disease. Unfortunately, the exact underlying molecular mechanisms that cause imatinib-resistant mutations in BCR–ABL are not yet known. The findings by Jiang et al. (8) reported in this issue describe the highly unstable state of the lin−CD34+CD38− stem cell population in CML and the propensity of these cells to develop mutations, even before BCR–ABL–targeted therapy. Previous data by Copland et al. (5) suggest this stem cell population to be the source of cells that can lead to hematologic relapse. However, they did not demonstrate the occurrence of new BCR–ABL kinase mutations. This study suggests that this stem cell population serves as a reservoir for chemoresistant CML cells. Novel and clinically relevant mutations within the BCR–ABL kinase domain were found to preexist in lin−CD34+CD38− CML cells and were increased within 3–5 weeks of in vitro culture. This finding was supported by studies of key protein markers of CML, demonstrating that there were no changes in the expression of the BCR–ABL oncoprotein or phosphorylation of its target CrkL, either in the presence or absence of imatinib. Whether the previously described amplification of the BCR–ABL gene is a major mechanism of drug resistance is controversial (9,10), and it was not observed in this study. In addition, Jiang et al. (8) found more than 70 different mutations in the BCR–ABL kinase domain, accompanied by a 30-fold increase in the transcription of the BCR–ABL gene. However, the causal relationship between these two events is not entirely clear. Particularly interesting is the divergence in the propensity toward the development of newly acquired mutations in the kinase domains between c-ABL in normal stem cells (low), compared with BCR–ABL in leukemic stem cells (high). Therefore, the change in mutation rate is not a function of environmental conditions, such as the high oxygen atmosphere during in vitro cell culture, but is rather a result of oncogenic transformation within the stem cell population. These data would ultimately be suggestive for a role of early CML progenitors as the source of cell populations with newly acquired imatinib-resistant BCR–ABL mutations. A deeper understanding of the mechanisms contributing to these mutations in CML would be useful in designing future more effective therapeutic agents targeting the lin−CD34+CD38− stem cell population.

The data by Jiang et al. (8) are consistent with a model whereby mutations in the BCR–ABL kinase domain occur spontaneously. Thus, in chronic-phase CML, cancer stem cells are already genetically unstable. The majority of mutations found were point mutations; gene amplifications, at least in this model system, did not occur at a detectable rate. In this context, the formation of reactive oxygen species is of particular relevance to the development of drug resistance, due to the fact that ROS can lead to DNA damage (11). Previous studies indicate that hyperactive glucose metabolism is the major pathway that leads to the increased formation of ROS in BCR–ABL–transformed cells and that the ROS originate largely in the mitochondria (12,13). It has been hypothesized that the induction of DNA damage through ROS, in combination with BCR–ABL–dependent mechanisms, leads to altered or increasingly error-prone DNA repair in CML (14–16), ultimately contributing to genomic instability and thus imatinib resistance. If this model holds true, one can envision that targeting either elevated oxidative stress or altered DNA repair may be sufficient to decrease the rate of genomic mutations, in particular, in the BCR–ABL kinase domain in lin−CD34+CD38− CML stem cells.

The characterization of aberrant DNA damage and DNA repair mechanisms in CML cells is essential to understanding this process and learning how to inhibit it. The ultimate goal is to develop effective novel targeted therapies for CML that improve survival. The data by Jiang et al. (8) place the target cells within the very early lin−CD34+CD38− CML stem cell population. Drug treatment itself does not seem to be a predetermining factor in causing specific mutations but rather is expected to select for specific subpopulations of these genetically unstable CML cells. Thus, a future challenge will

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be to devise approaches that overcome drug resistance within these cells without selecting for additional drug-resistant populations. An important question that needs to be clarified is whether BCR–ABL itself commits these cells to oncogene addiction. In this case, improved ABL inhibitors may be sufficient to cause long-term remission. Nevertheless, it is quite likely that combination therapies including BCR–ABL targeting drugs will have greater success. A challenging obstacle to any approach may be the likelihood that CML progenitors “hide” within the stem cell niche.

References


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