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The hematologists’ Maltese Falcon

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Insights into cell stage–specific effects will shed light on pathogenesis and more successful therapies of BCR-ABL leukemia. In this issue of Blood, Schemionek and colleagues use a conditional BCR-ABL transgenic mouse model to identify properties of the CML-initiating cell.1

The precise identity of the CML-initiating cell has been elusive, like the fictional Maltese Falcon. Properties of the CML-initiating cell include limited self-renewal, resistance to tyrosine kinase inhibitor, and ability to proliferate and differentiate. Professional illustration by A. Y. Chen.

The Knights Templar of Malta paid tribute to Charles V of Spain by sending him a golden falcon encrusted with jewels. Pirates stole this priceless token and the fate of the Maltese Falcon remains a mystery, still invoked by films and novels.

Our story begins more than 150 years ago when John Hughes Bennett in Edinburgh and Rudolf Virchow in Berlin described, at autopsies, enlarged spleens in men who had been ill for 1 to 2 years and died after severe nosebleeds.2 Their blood appeared different. To Bennett, it looked like pus and he called it pyemia. To Virchow, it was white blood or leukemia (leukämie). We now call their subjects’ condition chronic myeloid leukemia (CML). Since then, the abnormal chromosome has been identified, the affected genes isolated and characterized, mouse models created, and drugs approved.3 All have come together to truly make CML a chronic disease, not a fatal one.

No cancer is better understood at the molecular level than CML.4 Yet, like the fate of the Maltese Falcon, mysteries remain. Is Bcr-Abl the only genetic lesion required for chronic-phase CML? Can tyrosine kinase inhibitor therapy cure CML? How does p210 Bcr-Abl result in CML, but p190 in acute lymphoblastic leukemia? Why does the oncogenic Bcr-Abl promote proliferation and intact differentiation? Is there a dysfunctional relationship between the leukemic clone and its microenvironment? The CML-initiating cell lies at the heart of these mysteries (see figure).

By making a binary transgenic mouse where BCR-ABL expression is conditional upon withdrawal of tetracycline, the investigators created a mouse model that comes closest to mimicking human CML.5 Using their mouse model, they now report on properties of the CML-initiating cell: (1) CML–like disease is transplantable using LSK (lin−Sca−1−c–kit+) cells or unfractionated bone marrow; (2) leukemic granulocytes or progenitors do not initiate or enhance the CML–like disease; and (3) serial transplantation reduces the development of CML–like disease.

One finding of clinical value was that the transplantation of unfractionated bone marrow enhanced CML–like disease. This suggests that BCR-ABL induces differentiation of the CML stem cell belonging to the LSK compartment. By decreasing self-renewal capacity, BCR-ABL expression might be exploitable for therapy. How can clinicians modulate the administration of tyrosine kinase inhibitor therapy to better eliminate the CML-initiating cell? This mouse model provides the best available in vivo system to either fine-tune a single drug or design a more potent combination of agents. It may be further adapted by adding a genetic lesion that induces an accelerated phase or blast crisis, where a single tyrosine kinase inhibitor inhibitor is not so effective and the need for a more effective combination of agents is great.

Part of their approach in phenocopying human disease was to use the 3’ enhancer of the murine stem cell leukemia (SCL) gene. Because the naturally occurring human 5’ regulatory elements of the BCR-ABL fusion gene could have different expression patterns in human hematopoietic and stromal cells, some of the observed properties may be approximate. Mice strains are highly inbred. The influences of epigenetics, polymorphisms, and noncoding RNAs are poorly understood in the context of mouse modeling of BCR-ABL disease.

Because Bcr-Abl sets off a chain reaction of complex signaling events, some of their conclusions may be approximate. For instance, their conclusion that Bcr-Abl differentiates the long-term hematopoietic stem cells may be due to other effects such as cellular senescence, oxidative stress, or metabolic exhaustion.6 The investigators also conclude that CML disease is cell autonomous. Still, murine hematopoietic stem cell compartments may not perfectly mimic human ones, and their stroma may behave or cooperate differently from that of human origin. The story has become more complex with identification of Hedgehog and Wnt/β-catenin in maintaining CML-initiating cell stemness.7,8 These morphogens function...
The adulthood of MRD detection in MCL

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In this issue of Blood, Pott and colleagues correlate clinical outcome and MRD results in MCL. The analysis by real-time quantitative PCR of 259 patients included in 2 international randomized trials indicated MRD as an independent outcome predictor. The good large-scale applicability and high predictive value indicate that MRD detection is ready to be assessed as a decision-making tool in MCL.

The prognostic value of minimal residual disease (MRD) detection by polymerase chain reaction (PCR)-based methods in mature lymphoid tumors has been debated over nearly 2 decades. Following the seminal works of Gribben et al in autografted follicular lymphoma (FL) patients, the prognostic role of MRD has been demonstrated in many different mature lymphoid neoplasms and is now well established in multiple myeloma, FL, and mantle cell lymphoma (MCL). From a clinical perspective, the contribution of MRD studies has been particularly prominent in MCL. In the pre-rituximab age, the specific chemoresistance of MCL patients was outlined by their extremely low rate of molecular remission as opposed to FL patients. The subsequent improvement of treatment paradigms in MCL was heralded by MRD studies. Magni et al showed that the introduction of high-dose Ara-C and rituximab produced an unprecedented level of cytoreduction. Later, Pott et al demonstrated the predictive value of MRD monitoring in a retrospective analysis of 29 patients. Finally, Andersen et al showed the feasibility of preemptive treatment of molecular relapse in reducing the risk of overt clinical recurrences. Over this long period of time, methodological approaches have also evolved as qualitative PCR has been implemented and often substituted by real-time quantitative PCR.

The prognostic role of MRD is thus fairly established in mature lymphoid tumors. Nevertheless, concerns on its use for decision making are still widespread among clinicians due to the following issues: (1) patient series are small, often retrospective, and arising from single-center experiences; (2) MRD results can be treatment-biased (ie, some treatments might have superior molecular performances in the absence of a real clinical benefit); (3) the value of MRD is well documented in the autologous stem cell transplantation (ASCT) field but needs to be proved in the context of conventional therapy; (4) MRD assesses disease kinetics exclusively in peripheral blood (PB) and bone marrow (BM), but is unable to monitor disease evolution in nodal sites; (5) even if potentially useful, careful molecular monitoring is too cumbersome to be performed in the context of large, prospective phase 3 trials; and (6) MRD detection is not a standardized tool and comparability among different institutions has not been proven.

The work of Pott et al addresses several of the previously mentioned points. MRD was included here as a secondary endpoint in the context of 2 large international phase 3 trials (NCT00209222 and NCT00209209 [www.clinicaltrials.gov]) on a panel of 259 patients, representing a major sample size escalation compared with previous studies. The population included young and elderly patients. Treatment modalities included both conventional and ASCT-containing programs. The 90% success rate in obtaining a PCR-amplifiable tumor-specific marker in such multicenter (and multinational) context confirms the broad applicability of MRD in MCL. MRD proved predictive in all disease contexts and appeared to be unbiased even in the setting of maintenance treatment. The good prognostic discrimination observed in the elderly trial is a clear indication that the value of MRD monitoring is not restricted to specific ASCT-based treatment schedules. The article also focuses on the value of different tissue sources with respect to MRD analysis. Whereas MRD levels were comparable in BM and PB at diagnosis, disease clearance appeared more effective in PB. This indicates that MRD detection in the BM is a very effective sensor of global disease activity and not a mere indicator of local persistence of residual tumor burden. Nevertheless, the growing number of patients who have been assessed for MRD in this and other studies will allow verifying whether the few relapses arising among PCR-negative patients display specific clinical peculiarities compared with those heralded by PCR-positive results.

There are some limitations to this study. The overall population enrolled in the 2 trials of the European MCL Network is wider compared with the population analyzed in the report, as a large proportion of patients are still under evaluation. The 2 randomized trials are still blinded, preventing a detailed evaluation...
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