Hsc70 and Bag1 could be mapped at a finer level by point mutagenesis of BCR-ABL. A more complete characterization of the evolution from immature to mature forms of BCR-ABL needs to be undertaken. There is also the following curious (and at first glance, contradictory) observation. Inhibition of Hsp90 leads to more Hsc70 being bound to BCR-ABL which should lead to the oncprotein being stabilized/protected. However, Hsp90 inhibition leads to a reduction in the amount of detectable BCR-ABL protein.

Although most of the experiments concerned the p190 form of BCR-ABL that causes acute lymphoblastic leukemia (ALL), some of the important findings were also shown to be valid for the p210 form of BCR-ABL that is seen in the majority of patients with CML. In the clinical context of this leukemia, some aspects of the data call for pondering. Thus, the authors speculate that the structure of the BCR-ABL protein itself, rather than its kinase activity, is required for BCR-ABL to bind Bag1. If this is the case, it is intriguing that imatinib treatment abolishes Bag1 binding and BCR-ABL degradation completely (as shown in Figure 3A of their article). Similarly, the contention that the binding of the T315I BCR-ABL mutant protein to Bag-1 is due to this mutant being less structurally mature than wild-type BCR-ABL still needs to be demonstrated. Even more important is the apparent contradiction between the presence of mature BCR-ABL in CML stem cells and their lack of imatinib responsiveness. Further investigations in this area will hopefully clarify these questions.

The study by Tsukahara and Maru goes a long way toward understanding the nature of the complex interactions between the various protein–processing factors and their role in determining the fate of the BCR-ABL protein after its synthesis. As such, it provides a wealth of potential new CML targets, from Hsc70 and CHIP antagonists, to Bag1 agonists, or a combination of both.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Comment on Maes et al, page 3635

BMP-2: a culprit for anemia in myeloma

Heinz Ludwig WILHELMINENSPITAL, CENTER FOR ONCOLOGY AND HEMATOLOGY

Maes and colleagues1 have found increased BMP-2 in the blood of multiple myeloma patients as an important stimulator of hepcidin in addition to other well-known mediators of hepcidin induction. These findings were obtained by transfection of human liver HuH7 cells with reporter constructs for the hepcidin promoter carrying either mutations in BMP-response elements or in STAT3-binding sites. Although most of the experiments concerned the p190 form of BCR-ABL that causes acute lymphoblastic leukemia (ALL), some of the important findings were also shown to be valid for the p210 form of BCR-ABL that is seen in the majority of patients with CML. In the clinical context of this leukemia, some aspects of the data call for pondering. Thus, the authors speculate that the structure of the BCR-ABL protein itself, rather than its kinase activity, is required for BCR-ABL to bind Bag1. If this is the case, it is intriguing that imatinib treatment abolishes Bag1 binding and BCR-ABL degradation completely (as shown in Figure 3A of their article). Similarly, the contention that the binding of the T315I BCR-ABL mutant protein to Bag-1 is due to this mutant being less structurally mature than wild-type BCR-ABL still needs to be demonstrated. Even more important is the apparent contradiction between the presence of mature BCR-ABL in CML stem cells and their lack of imatinib responsiveness. Further investigations in this area will hopefully clarify these questions.

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group of related proteins that not only induce formation of cartilage and bone but now are also regarded as multifunctional cytokines. BMP-2, as 1 representative of the 20 hitherto described BMPs, also plays a key role in osteoblast differentiation and induces apoptosis in myeloma cell lines and in primary samples from patients with myeloma. The definite origin of BMP-2 production in myeloma is uncertain, although it is likely to derive directly from bony tissue such as chondrocytes1 and possibly from bone marrow stroma cells. Increased BMP-2 production may reflect a counterbalance to excessive bone degradation and a defense mechanism against the proliferating myeloma cells by down-regulation of Bcl-xl, by cell-cycle arrest through up-regulation of the cyclin kinase inhibitors p21 and p27, and by hypophosphorylation of the retinoblastoma protein. Furthermore, BMP-2 has been shown to result in immediate inactivation of STAT3 leading to the disruption of the IL-6-signaling pathway.3

In myeloma, increased hepcidin levels have been reported by several investigators.2,6 Hepcidin plays an important role in inflammation by restricting intestinal iron absorption and macrophage iron release. Its expression is modulated in response to body iron stores, hypoxia, and infectious and inflammatory stimuli. Among the inflammatory cytokines, IL-6 is an effective inducer of hepcidin but according to the results of Maes et al, BMP-2 seems to be an even more important hepcidin stimulator in patients with myeloma. Increased hepcidin levels result in iron-restricted normochromic anemia characterized by hypoferremia, normal to increased ferritin, and reduced transferrin saturation.7 Body iron stores usually are normal or increased, but due to the described alterations the available iron cannot be used by the erythropoietic marrow. This so-called anemia of chronic inflammation is probably the most frequent cause of anemia in multiple myeloma. Other frequent causes or contributory factors of anemia in myeloma are decreased erythropoietin production as a consequence of clinical apparent or subclinical renal impairment, reduced sensitivity of erythroid precursors to erythropoietic stimuli, suppression of erythropoiesis by antmyeloma therapy, dilutional anemia due to hypervolemia, and, in some cases, direct myeloma cell–mediated apoptosis of erythropoietic precursors.8 Overall, approximately 50% to 60% of patients present with overt anemia at diagnosis and up to 90% develop anemia during myeloma therapy. As the available treatment options for chronic anemia of myeloma—such as red cell transfusions, erythropoietic agents, or intravenous iron supplementation—are less than optimal, the question arises of whether the results of this study can be exploited for the design of new treatment concepts. Inhibition of BMP-2 should reduce hepcidin production but is unlikely to result in complete abrogation of hepcidin stimulation because of the increased production of various cytokines with hepcidin-inducing activity. In addition, inhibiting BMP-2 may be counterproductive, given its important role in osteoblast, cartilage, and bone formation and possibly, even more importantly, its antmyeloma activity. Subject to these considerations, hepcidin seems to be the logical target for therapeutic intervention, because high hepcidin expression is sufficient to cause anemia and resistance to endogenous erythropoiesis.9 In fact, hepcidin depletion by neutralizing antibodies or by hepcidin small-interfering RNA was shown to restore normal hemoglobin levels in a mouse model of anemia of chronic inflammation when applied in combination with erythropoietic agents.10 Other approaches to hepcidin inhibition are inhibitors of the stimulatory pathways for hepcidin transcription or strategies that block the effect of hepcidin on its only known cellular target ferroportin. Progress in this area could revolutionize treatment of anemia of chronic inflammation and, hence, treatment of the most common cause of anemia in myeloma.

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Comment on Chen et al, page 3660

FNAIT: the fetus pleads guilty!

Cécile Kaplan Institut national de la transfusion sanguine

Fetal/neonatal alloimmune thrombocytopenia (FNAIT) resulting from fetal platelet destruction by maternal alloantibodies is the most common cause of severe fetal thrombocytopenia and of neonatal thrombocytopenia in maternity wards.1 The pathophysiology is largely unknown. The fetus has long been considered as an “innocent bystander.” In this issue of Blood, Chen and colleagues, using murine models, demonstrate that the fetal, not maternal, major histocompatibility complex class I–related neonatal Fc receptor (FcRn) is implicated in the transplacental transfer of maternal antibodies and show that monoclonal antibody specific to FcRn may be effective in this disease.2 FNAIT (1/1000 live births) is usually discovered incidentally.3 The complication most feared is intracranial hemorrhage, leading to death or neurologic sequelae.4 If the fetus in a subsequent pregnancy is also platelet antigen incompatible, the condition is usually more severe, so antenatal management has been proposed with weekly maternal administration of intravenous immunoglobulins (IVIG).5 This treatment is relatively effective. However, this therapy relies on a human–derived product; it is expensive and in some cases...
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