Comment on Waning et al, page 320

Culling for survival

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In this issue of Blood, Waning and colleagues investigate the function of the ubiquitin ligase Cul4A, known for its involvement in protein degradation and histone modification. The present study reveals an essential requirement for Cul4A in hematopoiesis.

The continuous generation of short-lived blood cells depends on tightly controlled proliferation and differentiation of hematopoietic progenitors. Changes in gene expression are part of this developmental program, orchestrated by a combination of epigenetic, transcriptional, and RNA-based events. However, the aforementioned molecular processes only affect transcription and translation; they cannot eliminate already synthesized gene products. So, how does the counterpoint to gene expression—the regulation of protein destruction—contribute to hematopoiesis?

To address this question, Waning and colleagues at Kristin Chun’s laboratory have generated an inducible knockout of Cullin 4 (Cul4A), a master regulator of protein degradation. Originally named for their ability to select proteins for removal,1 cullins form the backbone of modular complexes that selectively transfer ubiquitin onto target proteins (see figure). Once modified by multiple ubiquitin molecules, the substrate proteins are then recognized and destroyed by the proteasome. Cul4A has been linked to DNA synthesis and repair as well as to transcriptional regulation. A previous study has indicated that Cul4A influences differentiation of hematopoietic progenitors.3 However, with the embryonic lethality of the homozygous Cul4A knockout and only mild signs of haploinsufficiency, the specific contribution of this molecule to adult hematopoiesis has remained elusive.4

Here, the authors have generated a conditional knockout of Cul4A driven by interferon-inducible Cre recombination. Upon deletion, animals develop a striking pancytopenia. They die within a few days, with widespread signs of apoptosis in rapidly proliferating tissues such as the intestine and the bone marrow.

The described phenotype following Cul4A excision is impressive, but we still lack a molecular and cellular explanation for the rapid loss of hematopoietic cells. Areas for future research therefore include the identification of the substrate protein(s) of Cul4A, whose lack of ubiquitination in the knockout in the knockout mice is responsible for the observed bone marrow failure. The authors propose that p27 and Cdt1 accumulation in Cul4A knockout cells are to blame for induction of apoptosis, but this point remains unproven. In particular, the possibility of a nonproteolytic function of Cul4A (eg, histone modification) has not been addressed. A second avenue for further research would pursue the precise definition of those cells affected most by Cul4A deletion. The data provided by Waning and colleagues suggest that rapidly proliferating progenitor cells are more susceptible to loss of Cul4A than quiescent stem cells. Third, given that it is ubiquitously expressed, how does the deletion of Cul4A affect other organs? The tissue-specific consequences of protein degradation have recently been exemplified by the observation that cullin-mediated removal of a particular transcription factor promotes differentiation in neurons, whereas the very same elimination process induces malignant transformation in the epithelial lineage.3 In addition to its physiological function, Cul4A has also been implicated in oncogenesis; its gene is amplified in several cancers, and mutations in the substrate recognition module DDB2 cause xeroderma pigmentosum, a disease characterized by DNA-repair defects.

In conclusion, the conditional Cul4A mouse model provides a powerful tool for
studying the role of cullin-mediated ubiquitination in vivo. The investigations of Wang et al. have already revealed essential pathways in hematopoietic and other regenerating tissues; there are likely more to be discovered.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

Allografting in ALL: the net widens

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The introduction of the GVL effect is the single most efficacious therapeutic intervention in the management of patients with ALL who are in complete remission.

Three decades have passed since the first report in humans of the graft-versus-leukemia (GVL) effect, which was most significant in patients with acute lymphoblastic leukemia (ALL). The relapse rate was 2.5 times lower in allogeneic marrow recipients with graft-versus-host disease (GVHD) than in patients without GVHD. Despite this early report, the incorporation of allogeneic transplantation into clinical practice in ALL has been slow, especially for patients in first remission. Initially, it was employed only for ALL patients with the Philadelphia chromosome and was followed by several reports on the use of allogeneic transplantation for high-risk ALL patients in first remission. Recently, a very large prospective trial, the international Medical Research Council/Eastern Cooperative Oncology Group (MRC/ECOG) study, reported on the benefit of allografting for adult patients with ALL in first complete remission, with the greatest effect seen in patients with standard risk. In older patients, high treatment-related mortality (TRM) abrogated the beneficial antileukemic effect due to GVL.

All of these investigations used HLA-matched siblings. The increasing use of matched unrelated donors in ALL has given further hope to the majority of patients who do not have a sibling donor.

Marks and colleagues in this issue of Blood have addressed this matter by reporting on an observational study conducted by the Center for International Blood and Marrow Transplant Research (CIBMTR) on 169 unrelated donor transplants in adults with Philadelphia chromosome-negative ALL in first complete remission. More than 90% of patients were at high risk. Approximately half of the patients had acute GVHD and more than 40% of patients had chronic GVHD. The TRM was about 40%. Despite this, about 40% of patients appeared to be long-term survivors, which is significantly better than what one would expect from high-risk ALL patients who would be treated without transplantation. As the authors themselves note, caution must always be exercised when interpreting retrospective data from registries, and historical comparisons have similar pitfalls. Nevertheless, this is an important study; the data provided by it confirm the feasibility and importance of the antileukemic effect of allogeneic transplants when using matched unrelated donors. Clearly, this approach is encouraging and needs to be pursued in prospective studies.

At least 2 major issues remain. First, why confine this approach to patients at high risk? Given that the best data on the use of allogeneic transplantation in first complete remission in ALL have been for patients at standard risk, the potential for increasing the donor pool to include matched unrelated donors should be studied in this more favorable risk category. Second, the lack of a significant survival benefit for older patients at high risk in the international ALL trial was due to the high TRM in older adults, much like in the report from the CIBMTR. While there are increasing data on the use of reduced-intensity allogeneic transplantation in AML, the data on the use of such conditioning regimens in ALL are scanty. As the majority of adult patients with ALL are older than 40 years of age, this modality, both for related and unrelated donor transplants, is an attractive concept that must be prospectively evaluated, especially in light of the fact that the incidence of unfavorable cytogenetics, such as the Philadelphia chromosome, increases with age and approaches 50% in patients with B-lineage ALL who are older than 50 years of age.

While the pendulum is swinging to more fully embrace the GVL effect in ALL in first remission, this must be done cautiously and in carefully controlled prospective clinical trials.

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