reversible neutropenia, anemia, and thrombocytopenia. During the observation period, 2 patients were diagnosed with fatal secondary myelodysplastic syndrome/acute myeloid leukemia and 13 patients had reduced left ventricular shortening fraction. However, only 1 of them required cardiac medication. Long-term toxicity, mainly the risk of secondary solid tumors, cannot be fully judged yet because the median observation is still too short for reliable conclusions. Other toxicity such as infertility—a relevant problem after BEACOPP—was not consistently documented.

Thus, upfront treatment intensification using $BEACOPP_{escalated}$ followed by a less intensive consolidation in early responders produced impressive results without unexpected acute toxicity in children and adolescents suffering from high-risk HL.[2] This finding does not come as a surprise because a significant portion of patients included in this trial (48%) were adolescents aged 15 to 21 years. Adolescent HL patients (usually defined as those between 15 or 16 and 21 years of age) do not differ substantially from young adult HL patients (age up to 45 years) with regard to clinical presentation, distribution of histologic HL subtypes, and other general aspects and are thus candidates for treatment strategies developed for adults.[6,7]

An approach similar to the one reported by Kelly and colleagues was recently evaluated by Avigdor and coworkers in a group of 45 adult patients diagnosed with advanced HL.[8] Patients received early interim PET after 2 cycles of $BEACOPP_{escalated}$ and those with a good response completed treatment with 4 cycles of ABVD. In the PET-negative early responders (31/45), 4-year progression-free survival rate was 87%, indicating that this strategy does not seem to compromise treatment results while side and late effects might be substantially reduced. However, the number of patients included in this analysis is too small for more general conclusions.

In contrast to adolescents, young pediatric HL patients usually show differences in the distribution of histologic subtypes and other more general aspects that might argue for the use of protocols specifically developed for children. Examples include OEPA (vincristine, etoposide, prednisone, adriamycin) and ABVE-PC (adriamycin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide).[9,10]

In conclusion, the data reported by Kelly and coworkers suggest that $BEACOPP_{escalated}$ represents a viable treatment option in pediatric and adolescent high-risk HL patients. However, to prevent overtreatment, whenever possible, the use of this protocol should be combined with stratification strategies such as interim PET.

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

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● ● ● HEMATOPOIESIS & STEM CELLS

Comment on Dutt et al, page 2567

Drawing to a Diamond flush

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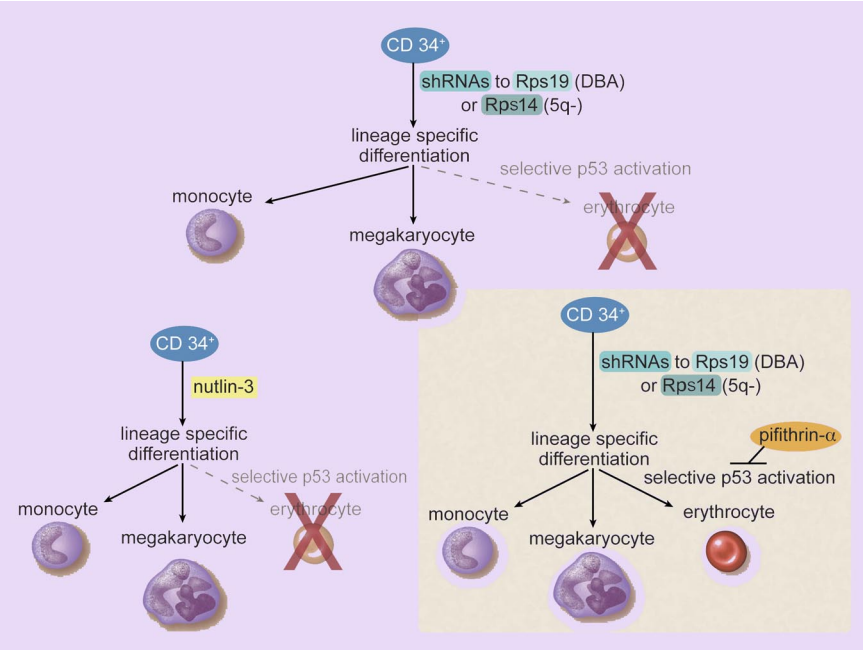
In this issue of *Blood*, Dutt and colleagues address the selective effect of ribosomal protein haploinsufficiency on erythroid development observed in congenital Diamond-Blackfan anemia (DBA) and acquired 5q− syndrome.[1] Their findings reveal a selective induction of p53 in the erythroid lineage in response to reduced expression of ribosomal proteins affected in these diseases. Moreover, the selective effect on erythropoiesis can be mimicked by activating p53 with the compound nutlin-3 and prevented by pifithrin-α, an inhibitor of p53 activation.

Diamond-Blackfan anemia is a rare congenital hypoplastic macrocytic anemia that typically presents in the first year of life. The hypoplastic anemia is associated with a dearth of erythroid progenitors reflecting their enhanced apoptosis. The first DBA gene was identified on the basis of a balanced translocation in a DBA patient.[2] One can only assume that the jubilation associated with the identification of the gene at this translocation breakpoint must have been tempered when it was shown to encode ribosomal protein S19. To borrow a phrase used frequently during the ongoing financial crisis, a ribosome was generally considered too big (and too ubiquitous) to fail, and so was presumably too vital for cellular processes to give rise to a disease exhibiting the tissue selectivity of DBA as opposed to an early embryonic death. Thus, while giving the ribosome its due as a potential target of pathogenic lesions in DBA, Draptchinskaia et al also suggested that some unknown function of Rps19, apart from its role as a structural component of the ribosome, could account for its selective effect on erythropoiesis.[2] The subsequent identification of 8 other DBA genes, all of which encode a seemingly random assortment of ribosomal proteins, argued against a common extra-ribosomal target in DBA pathophysiology.[3] The case for the ribosome as a molecular target in DBA became overwhelming when Ebert and colleagues showed another ribosomal protein gene, *RPS14*, was responsible for the macrocytic anemia observed



The effects of decreased expression of ribosomal proteins and p53 activation on myeloid differentiation. Top, reduced expression of Rps19 and Rps14, ribosomal proteins affected in Diamond-Blackfan anemia and 5q− syndrome, respectively, selectively affects erythroid differentiation from human CD34+ progenitors. Bottom left, treatment with nutlin-3, which results in p53 activation, mimics the effect of reduced ribosomal protein expression. Bottom right, pifithrin-α, an inhibitor of p53 activation, rescues the effect of reduced ribosomal protein expression on erythropoiesis. (Professional illustration by Debra T. Dartez.)

in 5q− syndrome, a subtype of myelodysplastic syndrome.[4]

Reduced expression of ribosomal proteins affected in DBA and 5q− syndrome has been shown to disrupt ribosome assembly.[4-5] Defects in ribosome assembly in turn, have been shown to lead to p53 activation mediated through the interaction of liberated ribosomal proteins with the central mediator of p53 stability, MDM2.[6] Thus, an emerging paradigm for DBA pathogenesis begins with a disruption of ribosomal subunit assembly induced by ribosomal protein haploinsufficiency. One or more ribosomal proteins now redirected from their normal fate as structural components of the ribosome interact with MDM2, inhibiting its ubiquitin ligase activity toward p53, leading to p53 stabilization and activation. What remained to fill in this hand (model) was to determine whether such a pathway could show the necessary erythroid selectivity to potentially be responsible for the bone marrow failure observed in DBA and 5q− syndrome.

In this issue, Dutt et al use primary human bone marrow CD34+ cells induced to differentiate along different myeloid lineages in vitro to show that reduced expression of either Rps19 or Rps14 caused the selective induction of p53 in the erythroid lineage[1] (see top panel of figure). This induction appears to be mediated by Rpl11, which has been shown previously to be translationally up-regulated when the assembly of 40S subunits is disrupted.[7] Rpl11 synthesized in excess of that needed for ribosome assembly interacts with MDM2 (or HDM2 in human cells), leading to p53 stabilization and activation. Intriguingly, Dutt et al show that nutlin-3, a compound that binds to HDM2 and inhibits its association with p53, has a selective effect on erythroid differentiation similar to that of reduced expression of Rps19 and Rps14[1] (bottom left of figure). Further, pifithrin-α, which blocks transcriptional activation by p53, rescues the impaired erythropoiesis (bottom right of figure). This latter observation points to a potential therapy for the erythroid defect in DBA. As pointed out by Dutt et al, therapies directed at inhibiting p53 activation contain inherent risks and should not be considered lightly.[1]

Does our understanding of DBA pathophysiology based on the results of Dutt et al represent the equivalent of a royal flush, or is there room for continued refinement? One of the limitations of the report by Dutt et al is that their studies on the effects of reduced expression of ribosomal proteins examine cells of quite different proliferative potential.[6] Cells of the myelomonocytic lineage examined were largely quiescent, whereas the erythroid lineage was represented by earlier, more rapidly proliferating progenitors. Thus, at least part of the erythroid selectivity observed in the present study may relate to the proliferative state of the different cell populations studied. There also remains a continuing conundrum between emerging models for DBA and 5q− syndrome and a very similar model proposed for Treacher Collins syndrome (TCS). TCS is caused by a defect in ribosome synthesis linked to mutations in *TCOF1*, which affect RNA polymerase I transcription and the synthesis of ribosomal RNA. Similar to animal models of DBA, defects in mouse development caused by mutations in *TCOF1* are rescued by p53 inactivation.[8] Yet, unlike DBA and 5q−, individuals with TCS do not exhibit a macrocytic anemia.[9] Instead, it is the rapidly proliferating cells of the developing neuroepithelium and neural crest that are selectively affected in TCS. Thus, although the work of Dutt et al represents a major advancement in our understanding of the pathogenesis of DBA and provides potential avenues for therapeutic intervention, additional studies are needed are needed to complete our understanding of the unusual sensitivity of the erythron to ribosomal protein haploinsufficiency.

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

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