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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Traxler et al, page 1999

Novel phosphatase-based regulatory loop for HbF expression

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In this issue of *Blood*, Traxler et al[1] using a novel CRISPR-Cas12a–based screening platform, have identified protein threonine phosphatase A (PTPA)–PP2A phosphatases as novel upstream mediator of BCL11A regulating fetal hemoglobin expression.

In the last 2 decades, great efforts have been made in identifying pharmacologic inducers of fetal hemoglobin (HbF) production as therapeutic strategy for patients with either sickle cell disease (SCD) or transfusion dependent thalassemia (TDT).[2,3] A very recent outcome of these efforts has been the approval of cell therapies targeting BCL11A, the main regulators of HbF switching, which have resulted in curative values of HbF production for patients with either SCD or TDT.[2,3] Despite these impressive successes, there remains an urgent need for novel pharmacological therapies which can replicate the success and practicality of hydroxyurea without its side effects. Indeed, hydroxyurea is an inexpensive disease modifying agent, but its accessibility is still inadequate in low- and middle-incoming countries where the most patients with hemoglobinopathies live.[4]

Signal transduction pathways play a key role in the dynamic events involved in cell differentiation and maturation. Phosphatase/kinases are crucial components of cell-signaling machinery. Up to now, limited studies have systematically investigated the contribution of signal transduction pathways to Hb switching from HbF to adult Hb. Traxler et al used a 2-tier genetic screening approach with a novel CRISPR-Cas12a–based screening platform followed by a CRISPR-Cas9 domain screen to identify novel regulators of *HBG* expression. This approach highlights the technical advantage of CRISPR-Cas12a–based screening and validates a new molecular toolbox, which has wide applicability.[1] In the first step, the genome-wide screening identified 211 candidate genes. In the secondary screen, they focused on candidate genes, which might activate *HBG* expression when edited without impacting cell features. PTPA, a regulatory subunit of the serine-threonine phosphatase PP2A complex, was selected as promising candidate of BCL11A expression and further investigated in HUDEP-2 and $CD34^+$ cells derived from healthy donors. Engineered cells were used to carefully dissect the role of the individual components of the PTPA-PP2A complex. The authors showed that Cas9 disruption of PTPA enhanced HbF expression to a similar degree as targeting the disruption of BCL11A, a well-established strategy for gene therapy of hemoglobinopathies.[2,3] Thus, the data generated by Traxler et al set a new threshold for studying molecular signaling to reactivate HbF expression. Notably, both PTPA and PP2A are evolutionary preserved phosphatases in eukaryotic cells, supporting their biologic importance in cell homeostasis.[5]

Studies in other cell models showed that PTPA promotes the ATPase activity of PP2A.[6] To better understand PTPA signal transduction toward BCL11A, they generated genetic PTPA mutants and demonstrated the ATPase function to be critical for the suppression of BCL11a. These studies elegantly demonstrate that the PTPA-PP2A signaling network plays a crucial role in dephosphorylation of transcriptional factors targeting directly the BCL11A locus. Thus, PTPA-PP2A should be considered as a novel therapeutic target alone or in combination with other strategies to reactivate *HBG* expression. Traxler et al validate a new way to identify key player(s) involved in *HBG* silencing (CRISPR-Cas12a–based screening platform) and develop a new modality to modulate HbF expression. This work provides a 21st century validation of the motto *Aut inveniam viam aut faciam* ("I shall either find a way or make one," attributed to Francis Bacon, British philosopher and scientist, 1561-1626 AD) in the 400th anniversary year of Francis Bacon's death.

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