Stony Brook University

The Graduate School

Doctoral Defense Announcement

Abstract

Therapeutic targeting of early erythroid progenitors

By

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Healthy bone marrow produces immature blood cells — called stem cells and progenitor cells — which normally develop into mature, fully functional red blood cells. The early erythroid progenitor, burst-forming unit erythroid (BFU-E), is the first erythroid lineage committed progenitor and possesses substantial capacity to undergo expansion. This unique property of BFU-E has shown immense therapeutic potential and yet its regulators and underlying mechanisms of its expansion are unclear. Here, I have uncovered multiple regulators of BFU-E expansion and its potential mechanisms. Genetic as well as pharmacological inhibition of cholinergic acetylcholine receptor muscarinic 4 (CHRM4) and carbonic anhydrase 13 (CAR13) stimulated BFU-E expansion and differentiation. Furthermore, CHRM4 and CAR13 inhibitors alleviated anemic symptoms by promoting BFU-E expansion and producing more erythrocytes in splicing factor mutant mouse models of myelodysplastic syndrome (MDS), where chronic anemia is the major phenotype. Moreover, knockout mouse models of *Chrm4* and *Car13* up-regulated BFU-E expansion during stress erythropoiesis. Mechanistically, CHRM4 inhibition upregulates cAMP/CREB signaling axis and thereby promotes upregulation of many genes responsible for BFU-E expansion. CAR13 inhibition causes assimilation of its substrate bicarbonate with ammonia to support high expansion state of BFU-E. Altogether, I have identified multiple druggable regulators of BFU-E expansion which can be utilized to treat variety of anemias.

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(*If an outside member of the community would like to attend the defense, please contact the email address of the program director: martha.furie@stonybrookmedicine.edu)