REGIONAL CENTRE FOR BIOTECHNOLOGY
Seminar series

Hypoxia & Erythropoiesis in Health and Disease

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Abstract

Our molecular understanding of organismal responses to hypoxia has stemmed from studies of erythropoietin control by hypoxia that lead to discovery of transcriptional inducible factors, i.e. HIFs. The von Hippel Lindau (VHL) and prolyl 4-hydroxylase (PHD2) proteins are principal negative regulators of HIFs. Much has been learned from congenital defects of hypoxia sensing resulting in polycythemia. The homozygosity for polycythemia-causing hypomorphic VHL R200W mutation is endemic in Chuvashia and sporadic worldwide. Persistence of this mutation from the same founder originating ~50,000 years ago suggests an evolutionary advantage to the heterozygotes. Loss-of-function mutations of PHD2, and gain-of-function mutations ofHIF-2a also cause polycythemia.

Hypoxia increases erythrocytes (polycythemia) by enhancing HIFs. Upon return to normoxia, resulting polycythemia is overcorrected by the destruction of newly formed erythrocytes, a process termed neocytolysis; however, its mechanisms are unknown. We developed a neocytolysis mouse model and describe role of two HIF-regulated genesBNIP3L (which mediates removal of reticulocytes' mitochondria) and FOXO3A (whichregulates expression of antioxidant enzymes) in neocytolysis. During hypoxia, there is a reduction of FoxO3a-regulated catalase in newly-formed erythrocytes; on return to normoxia, there is an increase in mitochondrial mass with reduced Bnip3L transcripts and excessive generation of reactive oxygen species (ROS). We conclude that neocytolysis is caused by HIF-regulated changes of BNIP3L and FOXO3A leading to impaired mitochondrial clearance and ROS scavenging in those young erythrocytes that were produced during hypoxia. These two processes decrease erythrocytes by the preferential destruction of young, ROS-rich, catalase-low erythrocytes produced in hypoxia. Data in newborn humans suggest that neocytolysis also occurs after birth.

Uniquely among human populations, Tibetans do not exhibit increased hemoglobin concentration at high-altitude. We describe the first known genetic variant that contributes to this adaptive response, a high-frequency missense mutation of PHD2; PHD2D4E,C127S. We show that PHD2D4E,C127S originated ~8,000 years ago on the same haplotype previously associated with high-altitude adaptation. This variant exhibits a lower Km value for O2, suggesting that it promotes increased HIF degradation under hypoxia. PHD2D4E,C127S abrogates hypoxia-induced HIF-mediated augmentation of erythropoiesis and provides a molecular mechanism for the observed protection of Tibetans from polycythemia at high-altitude.