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Modern concepts in polycythemia from a 100 year-old syndrome

Polycythemia is a condition characterized by a net increase in the total number of blood cells. While there are options for limited management of this condition, including phlebotomy, there is no cure. In an effort to define the genetic defect underlying polycythemia with the supposition that this understanding will provide novel therapeutic intervention, Janus kinase 2 (JAK2) mutations were recently identified in a vast majority of individuals with polycythemia vera, the most common form of acquired polycythemia. Intriguingly, mutations in a different gene, von Hippel-Lindau (VHL), have been identified to cause Chuvash polycythemia, a congenital form of polycythemia. These seminal discoveries have led to the notion that at a minimum two distinct mechanisms or pathways are involved in the development of polycythemia. Contrary to this notion, we show evidence supporting an unexpected convergence of these seemingly unrelated pathways to underlie Chuvash polycythemia, and reveal a new complexity in the substrate specification of E3 ubiquitin ligases.