Physiologic adaptation to hypoxia results in stabilization of hypoxia-inducible transcription factors (HIFs) and enhanced transcription of target genes involved in processes such as angiogenesis, erythropoiesis, glycolysis, apoptosis, and cell proliferation. Here we report our findings in a transgenic mouse line that expresses high levels of HIF2a in both a tissue and time-specific manner. Upon activation of the HIF2a transgene under a global or renal tubular-specific promoter, mice exhibit a range of dramatic phenotypes that include: symptomatic polycythemia leading to CVA-associated death, baldness, liver microvesicular steatosis, and kidney cysts. Remarkably, when the transgene is turned off, many of the above phenotypes reverse with the hematocrit returning to normal and fur beginning to regrow within hours. Taken together, these results suggest that HIF2α has pleiotropic biologic roles in multiple tissue types of varying significance and severity that demonstrate rapid 'on-off' regulation. Analysis of this mouse model is of particular importance currently in order to better understand the effects and side effects of a new class of drugs known as Prolyl Hydroxylase Inhibitors; a recently approved treatment of renal anemia via induction of HIF-2a expression in the kidney. Additionally, we believe this model may reveal potential novel therapeutic pathways related to the modulation of the many HIF-2a induced phenotypes.