Neutrophilic inflammation plays an important role in inflammatory lung diseases but therapeutic targeting of neutrophil (PMN) persistence is lacking. PMN lifespan and function is regulated by hypoxia, a characteristic feature of inflamed tissues, via the HIF/VHL/ hydroxylase pathway, specifically hypoxia inducible factor-1α (HIF-1α) and prolyl hydroxylase-3 (PHD3). Targeting HIF-1α in myeloid cells impaired immune function, but PHD3 regulated PMN lifespan without affecting function. Given that PHD3 preferentially regulates HIF-2α, we investigated the role of HIF-2α in PMN-mediated inflammation.

Peripheral blood PMNs isolated from healthy volunteers and mice expressed HIF-2α and expression was enhanced by heat-killed bacteria. Using PMNs isolated from patients with active inflammatory arthritis (IA) we demonstrated significant upregulation of HIF2α mRNA (IA 92.9±30.3 vs. control 4.3±0.9 AU relative to ACTB, P<0.05) and protein (IA 0.26±0.05 vs. control 0.01±0.01 OD relative to F38, P<0.01) in circulating inflammatory PMNs. PMNs recruited to the airways of patients with COPD also displayed strong HIF-2α staining. The consequences of HIF-2α upregulation were examined using human PMNs from patients with gain-of-function mutations in the HIF2α gene. Neutrophils isolated from these patients had reduced rates of constitutive apoptosis. Recapitulation of the human HIF2α mutations in the orthologous HIF2α gene, eps40−, in zebrafish delayed resolution of inflammation in a tail injury model (24 hrs post injury, eps40−106±0.08 vs. KO 1.39±2.13). Impor-