Acute myeloid leukemia (AML) is the most common adult leukemia, and AML patients have a 5-year survival rate of <30%. We found frequent somatic mutations in ubiquitin proteasome system (UPS) genes by exome and RNA-seq of 140 clinical AML samples, with recurrent inactivating mutations in FBXO11, which codes the substrate-recognizing component of the SKP1-CUL1-F-BOX (SCF) ubiquitin E3-ligase complex. In our mouse marrow transplant model, Fbxo11 knockdown cooperates with AML1-ETO expression to initiate AML. These AMLs were serially transplantable, indicating the presence of leukemic stem cells (LSC). We found that FBXO11 loss in human cells promoted stem cell maintenance and myeloid differentiation in vivo, and also in xenotransplanted mice. Mass spectrometric analysis of FBXO11 co-immunoprecipitating proteins in K562 FBXO11 CRISPR/Cas9 knockout and control clones and identified mitochondrial protease LONP1 as a top interacting protein. We found that FBXO11 loss enriches primitive HSPC populations in our human model, identified novel candidate targets of FBXO11, and identified a novel link between the UPS and mitochondrial function. We are investigating mechanisms and effects of LONP1 regulation by FBXO11.