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A role for proteasome 26S subunit, non-ATPase 3 (PSMD3), in disease progression and drug resistance of myeloid leukemia.

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Acute myeloid leukemia (AML) patients with mutations in the FMS-like tyrosine kinase 3 (FLT3) gene can be treated with tyrosine kinase inhibitors (TKIs) targeting FLT3. However, many patients develop resistance or experience adverse side effects (1,2). The ubiquitin-proteasome system (UPS) plays an important role in regulating protein homeostasis, cell cycle progression, and apoptosis, thereby representing a potential target for combination therapies. However, similar to FLT3 TKIs, proteasome inhibitors are prone to adverse side effects and drug resistance, highlighting the need for alternative therapeutic strategies. We recently reported an oncogenic role for two members of the 19S regulatory complex, 26S proteasome non-ATPase subunits 1 (PSMD1) and 3 (PSMD3), in disease progression and drug resistance of chronic myeloid leukemia (CML) and various solid tumors (3,4). We hypothesized that these genes may also play an oncogenic role in AML.

TCGA data revealed that high levels of PSMD3 but not PSMD1 expression correlated with worse overall survival (OS) in AML (p=0.0029, Figure 1A-B). However, when we zoomed in on patients with FLT3 mutations, AML patients with high levels of PSMD3 mRNA expression had a sharp reduction in OS (FLT3+ AML, p=0.0015, Figure 1C-D). PSMD3 knockdown impaired colony formation of the FLT3-mutant AML cells lines, MOLM-13 and MOLM-14, correlating with increased OS in xenograft models. In contrast with our data in CML, PSMD3 knockdown had little effect on apoptosis or nuclear factor-kappa B transcription. Rather, mass spectrometry-based proteomics analyses revealed a potential role for PSMD3 in regulating energy metabolism. Consistently, PSMD3 knockdown resulted in reduced oxygen consumption rates in MOLM-14 cells. Altogether, PSMD3 may represent a novel molecular biomarker in FLT3+ AML and may be a novel target for combination therapies.

Biography:

Dr. Anna Eiring is an Assistant Professor in the Department of Molecular and Translational Medicine at Texas Tech University Health Sciences Center in El Paso, Texas, a Title V Hispanic-serving institution. Her lab focuses on disease progression and drug resistance in myeloid leukemias driven by constitutively active tyrosine kinases, namely BCR-ABL1-driven chronic myeloid leukemia (CML) and FLT3-mutated acute myeloid leukemia (AML). She has published nearly 50 papers on cancer biology and immunology, and has further interests in understanding the biology underlying worse outcomes for minority cancer patients.

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