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Intracellular oxidative stress contributes to the oncogenic potential of mutant FLT3 in acute myeloid leukaemia patients, and is a synergistic treatment target

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Leukaemic transformation of haematopoietic progenitors is a multistage process characterised by the overproduction of reactive oxygen species (ROS). AML patients diagnosed with recurring mutations to the FMS-like tyrosine kinase-3 (FLT3) commonly relapse after they achieve initial remission, succumb to a treatment resistant AML. FLT3-ITD (Internal Tandem Duplication) mutations are the most common genomic driver lesion, and are associated with the overproduction of ROS. Overproduction of ROS is induced by the activation of alternative metabolic pathways causing increased genomic instability through the oxidation of DNA bases, influencing clonal evolution. Importantly, ROS oxidises and inactivates key proteins indispensable for the regulation of growth and survival signalling pathways. To determine the cooperative mechanisms underpinning leukaemogenic growth and survival signalling, bone marrow trephine biopsies from AML patients at diagnosis were subjected high-resolution quantitative proteomic, phosphoproteomic and REDOX sequencing. Patients expressing FLT3-ITD mutations showed significantly increased expression of proteins directly responsible for the production of ROS. Oxidation and inactivation of tumour suppressor proteins particularly, protein tyrosine phosphatases (PTPs) directly downstream of FLT3, and directly upstream of STAT5 were seen compared to AML patients expressing wild-type FLT3. Proteins important in maintaining cellular homeostasis, such as antioxidants were differentially dysregulated between patient subtypes supporting the notion of REDOX dysfunction in FLT3-ITD+ AML patients. Reducing intracellular oxidative stress levels using novel clinically relevant compounds, reactivated intrinsic cellular defence systems, inducing selectively synergistic cell death when combined with FLT3-ITD inhibitors currently in clinical trials. Importantly, analysis of AML cells grown under conditions mimicking the bone marrow microenvironment, enhanced the anti-leukaemic efficacy of our novel therapies by reducing oxidative stress, decreased oncogene addition, highlighted the divergent metabolic requirements of AML blast cells in the bone marrow compared to the circulation. These studies suggest a mechanism of cooperation between oncogenic kinases, metabolism and oxidative stress to reveal a novel treatment paradigm currently under preclinical evaluation.

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