

METABOLIČKE PROMENE ZAVISNE OD REDOKS STATUSA SU U OSNOVI HEMIOSENZITIVNOSTI U ČELIJAMA LEUKEMIJE HL-60 I K562

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Oksidativni stres (OS) je odavno prepoznat kao centralni pokretač maligne transformacije i progresije. Kod leukemije, poremećena redoks ravnoteža i metaboličko reprogramiranje utiču na proliferaciju, diferencijaciju i preživljavanje ćelija, kao i na odgovor na terapiju. Povećana produkcija reaktivnih vrsta kiseonika (ROS) u ćelijama ne samo da podstiče razvoj bolesti već doprinosi i citotoksičnoj aktivnosti mnogih hemioterapeutika. U ovoj studiji, ispitali smo efekte dva leka, busulfana i melfalana, koji predstavljaju kondicionirajuću terapiju za transplantaciju hematopoetskih matičnih ćelija, na redoks status i metabolizam u dva različita metabolička *in vitro* modela, HL-60 (promijelocitna linija) i K562 (eritroleukemična linija). U ćelijama multiplog mijeloma melfalan indukuje proizvodnju ROS, smanjuje nivo glutaciona (GSH), indukuje oksidaciju proteina i lipida i aktivira antioksidativni odgovor posredovan Nuklearnim eritroidnim faktorom 2 (Nrf-2), ističući njegov uticaj na redoks regulaciju. U našoj studiji smo uporedili bazalne redoks markere u HL-60 i K562 ćelijskim linijama i procenili kako busulfan i melfalan moduliraju stvaranje ROS i citotoksičnost. Takođe smo ispitali i promene u metaboličkim profilima tretiranih ćelija kako bismo definisali promene izazvane lekovima u ključnim metaboličkim putevima, uključujući glikolizu, ciklus trikarboksilne kiseline (TCA), metabolizam aminokiselina i metabolizam glutaciona. Naši rezultati ukazuju da hemioterapija dovodi do redoks disbalansa i metaboličkog remodeliranja kod ćelijskih modela leukemije, ukazujući na potencijalne biomarkere hemiosenzitivnosti koji se mogu iskoristiti za poboljšane terapijske strategije kod lečenja mijeloidnih leukemija.

REDOX-DEPENDENT METABOLIC ALTERATIONS UNDERLYING CHEMOSENSITIVITY IN HL-60 AND K562 LEUKEMIA CELLS

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Oxidative stress (OS) has long been recognized as a central driver of malignant transformation and progression. In leukemia, disrupted redox balance and metabolic reprogramming critically shape cell proliferation, differentiation, and survival, while also influencing response to therapy. An excess of reactive oxygen species (ROS) over the antioxidant defense system (AOS) not only promotes leukemogenesis but also contributes to the cytotoxic activity of many chemotherapeutics. In this study, we investigated the effects of two drugs, busulfan and melphalan, used as conditioning therapy for hematopoietic stem cell transplantation, on OS and metabolism in HL-60 (promyelocytic) and K562 (erythroleukemic) cell lines, two different *in vitro* models with distinct metabolic profiles. In multiple myeloma cells, melphalan has been reported to induce ROS production, deplete glutathione (GSH), enhance protein and lipid oxidation, and activate the Nuclear factor erythroid 2 (Nrf-2)-mediated antioxidant response, underscoring its impact on redox regulation. Here, we compared basal redox markers in HL-60 and K562 cells and assessed how busulfan and melphalan modulate ROS generation and cytotoxicity. Importantly, we complemented these analyses with metabolomic profiling to capture drug-induced changes in key metabolic pathways, including glycolysis, the tricarboxylic acid (TCA) cycle, amino acid metabolism, and glutathione metabolism. Our results indicate that chemotherapy leads to redox imbalance and metabolic remodeling in leukemia cell models, representing potential biomarkers of chemosensitivity that can be exploited to develop improved therapeutic strategies for myeloid leukemias.