B-cell receptor triggers drug sensitivity of primary CLL cells by controlling glucosylation of ceramides

Janine Schwamb, Valeska Feldhaus, Michael Baumann, Michaela Patz, Susanne Brodesser, Reinhold Brinker, Julia Claasen, Christian P Pallasch, Michael Hallek, Clemens-Martin Wendtner & Lukas P Frenzel

Survival of chronic lymphocytic leukemia (CLL) cells is triggered by several stimuli, such as the B-cell receptor (BCR), CD40 ligand (CD40L), or interleukin-4 (IL-4). We identified that these stimuli regulate apoptosis resistance by modulating sphingolipid metabolism. Applying liquid chromatography electrospray ionization tandem mass spectrometry, we revealed a significant decrease of proapoptotic ceramide in BCR/IL-4/CD40L-stimulated primary CLL cells compared with untreated controls. Antiapoptotic glucosylceramide levels were significantly increased after BCR cross-linking. We identified BCR engagement to catalyze the crucial modification of ceramide to glucosylceramide via UDP-glucose ceramide glucosyltransferase (UGCG). Besides specific UGCG inhibitors, our data demonstrate that IgM-mediated UGCG expression was inhibited by the novel and highly effective PI3Kδ and BTK inhibitors CAL-101 and PCI-32765, which reverted IgM-induced resistance toward apoptosis of CLL cells. Sphingolipids were recently shown to be crucial for mediation of apoptosis via mitochondria. Our data reveal ABT-737, a mitochondria-targeting drug, as interesting candidate partner for PI3Kδ and BTK inhibition, resulting in synergistic apoptosis, even under protection by the BCR. In summary, we identified the mode of action of novel kinase inhibitors CAL-101 and PCI-32765 by controlling the UGCG-mediated ceramide/glucosylceramide equilibrium as a downstream molecular switch of BCR signaling, also providing novel targeted treatment options beyond current chemotherapy-based regimens.