Abstract

Diffuse large B-cell lymphomas (DLBCLs) represent the most frequent B-cell lymphoma and can be subdivided into two groups by their gene expression profile, the Activated B-cell-like (ABC) and the Germinal center B-cell-like (GCB) DLBCL subtype. Around 30% of all patients do not respond to standard immunotherapy or relapse, which highlights the need for further therapeutic options. Among the subtypes, ABC DLBCLs have a less favorable prognosis. ABC DLBCLs are characterized by chronic B-cell receptor signaling and concomitant NF-κB dependency. Since targeting NF-κB in patients is challenging due to severe side effects, we investigated other potential targets for ABC DLBCL treatment. We found elevated basal Ca^{2+} levels and NFAT activity in ABC and GCB DLBCLs. Surprisingly, chronic BCR signaling in ABC DLBCLs was not responsible for elevated Ca^{2+} levels and calcineurin activity. By use of the clinically approved drugs Cyclosporin A and FK506 we could show that calcineurin inhibition impaired survival of ABC but not GCB DLBCLs. In ABC DLBCL, decreased NFAT activity after calcineurin inhibition correlated with reduced expression of relevant target genes. Finally, we could demonstrate that calcineurin inhibitors synergized with a Mcl-1 inhibitor and the FDA-approved Bcl -2 inhibitor ABT-199 in inducing cell death in ABC DLBCLs. Collectively, we could show that the drugs Cylosporin A and FK506, both approved for treatment of autoimmune diseases, exhibited an anti-lymphoma effect, highlighting their potential for ABC DLBCL treatment.