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FOXO1 promotes resistance of Non-Hodgkin lymphomas to anti-CD20-based therapy

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Lack of remission or early relapse remains a major clinical concern in diffuse large B cell lymphoma (DLBCL) with a third of patients failing to respond to current regimens or relapsing with resistant disease. Genome and transcriptome sequencing studies have identified FOXO1 as one of the recurrent dtaduatarget of somatic mutations in DLBCL (1-3), associated with patient short survival. These mutations enhance FOXO1 nuclear localization and activity on target genes (4). Herein, we determine the role FOXO1 (wild type and mutated) on the expression of the rituximab-target, CD20. The effect of active mutated FOXO1 on CD20 expression was determined upon inhibition of AKT, exogenous expression of active myristolated AKT, and mutated FOXO1 at its N-terminal region. FOXO1 binding activity to CD20 promoter was assessed using various assays combined with an in Silico analysis of a publicly available Chip-Seq data. Our results show that the activation of FOXO1 using AKT inhibitors (MK-2206 and GDC-0068) led to a significant decrease of CD20 transcript and protein levels, which resulted in a significant resistance to rituximab-mediated complement-dependent cytotoxicity (CDC). Consistently, the overexpression of either wild -type or mutated FOXO1 repressed CD20 expression. Unlike the activity of exogenous wild type FOXO1 that can be inhibited by AKT1, the activity of mutated FOXO1-AAA (residues Thr24, Ser256 and Ser319 mutated to Ala, cannot be phosphorylated) markedly inhibits CD20 expression. Furthermore, CD20 levels remained high and unchanged by the DNA -binding defective mutant of FOXO1-H215R, suggesting a FOXO1 mediated regulation of CD20 transcription through FOXO1 binding to CD20 promoter, as confirmed by ChIP, EMSA and the analysis of ChIP-Seq data using anti-FOXO1 antibody. These results show that FOXO1 mutants that are insensitive to AKT1 kinase activity, effectively suppress CD20 expression in comparison to wild type FOXO1, through a binding to CD20 promoter. In summary, these results establish FOXO1 as an important determinant of cell response to complement-dependent rituximab-induced cytotoxicity. In addition, our observations indicate that the genetic status of FOXO1 together with its transcriptional activity needs further attention while designing rituximab-based regimens in the therapy of selected lymphomas.

Biography

Dr Zerrouqi is currenty developing new stategies to overcome cancer immune evasion and identifying factors that hinder the efficacy of current antibodies based therapies. He has a strong experience in cancer biology and cancer microenvironment of glioblastomas. He graduated from one of the Ivy ligue Universities of France , the Piere Marie Currie University at Paris, then, he moved to the Winship Cancer Institute of Emory University, Atlanta, USA where he studied the impact of specific genetic abberations on angiogenesis and tumor microenvironment. He then joined Helix Immunoconcology and the Department of Immunology of the Medical University of Warsaw to develop new strategies and translate last breakthroughs in immunooncology to the clinic.

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