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Targeting cholesterol synthesis increases chemoimmuno-sensitivity in chronic lymphocytic leukemia cells

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Cholesterol plays an important role in cancer development, drug resistance and chemoimmuno-sensitivity. Statins, cholesterol lowering drugs, can induce apoptosis, but also negatively interfere with CD-20 and rituximab-mediated activity. Our goal is to identify the alternative targets that could reduce cholesterol levels but doesn't interfere with CD-20 in chemoimmunotherapy of chronic lymphocytic leukemia (CLL). We used MEC-2 cells, a CLL cell line, and the peripheral blood mononuclear cells (PBMCs) from CLL patients, treated them with cholesterol lowering agents, and analyzed the effect of these agents on cholesterol levels, CD-20 expression and distribution, and cell viability in the presence or absence of fludarabine, rituximab or their combinations. We found that MEC-2 cells treated with cholesterol lowering agents (BIBB-515, YM-53601 or TAK-475) reduced 20% of total cellular cholesterol levels, but also significantly promoted CD-20 surface expression. Furthermore, treatment of cells with fludarabine, rituximab or their combinations in the presence of BIBB-515, YM-53601 or TAK-475 enhanced MEC-2 cell chemoimmuno-sensitivity measured by cell viability. More importantly, these cholesterol lowering agents also significantly enhanced chemoimmuno-sensitivity of the PBMCs from CLL patients. Our data demonstrate that BIBB-515, YM53601 and TAK-475 render chemoimmunotherapy resistant MEC-2 cells sensitive to chemoimmunotherapy and enhance CLL cell chemoimmuno-sensitivity without CD-20 epitope presentation or its downstream signaling. These results provide a novel strategy which could be applied to CLL treatment.

Biography

Chunfa Huang has completed his PhD from Xiamen University and Post-doctoral studies from Wake Forest University School of Medicine and University of Texas Southwestern Medical Center. He is highly trained in Lipid Metabolism and Cell Signaling as a graduate student and as a Post-doctor. Over the decades, his research area focuses on defining novel signaling pathways that regulate lipid metabolism and that are associated with human diseases including cancer, and has published more than 50 papers in reputed journals.

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