Glycomics & Lipidomics

Extended Abstract

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

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Abstract

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). CLL cell killing by rituximab requires cross linking of CD-20, which induces redistribution of CD-20 to lipid rafts. Lipid rafts are specialized microdomains of the plasma membrane that are enriched in sphingolipid and cholesterol, and play an important role in the initiation of many anticancer drug-induced signaling pathways and toxicological effects. Anticancer drugs are able to suppress cell growth and induce apoptosis of tumor cells through disrupting lipid raft integrity [32,47]. The redis-tribution of CD-20 may result in lipid raft disruption, activate or deactivate raft-associated proteins, such as death receptors and protein kinases in apoptotic pathway which are correlated with efficiency of complement-dependent cytotoxicity and antibody-complement-dependent cell-mediated cytotoxicity. Rituximab and other anti-CD-20 antibodies are currently key drugs in CLL chemoimmuno-therapy. Although statins have antitumor activity, they are clearly unsuitable for enhancement of chemoimmuno-sensitivity of lymphomas and leukemias.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. 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. Conclusion:Our data demonstrate that BIBB-515, YM53601 and TAK-475 render chemoimmuno-therapy resistant MEC-2 cells sensitive to chemoimmuno-therapy 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. Chronic lymphocytic leukemia (CLL) is the most preva-lent hematologic malignancy affecting Caucasian adults in Western countries. In the United States, about 15,000 new cases are diagnosed every year. CLL is characterized by the accumulation of mature CD5, CD19, and CD23 B-lymphocytes in peripheral blood, bone marrow, lymph nodes and spleen.

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