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Berberine downturns B-cell chronic lymphocytic leukaemia metabolism and cell cycle progression

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B-cell chronic lymphocytic leukemia (CLL) was believed to result from clonal accumulation of resting apoptosis-resistant malignant B lymphocytes. However, it became increasingly clear that CLL cells undergo, during their life, iterative cycles of re-activation and subsequent clonal expansion. Drugs interfering both with CLL cell survival and cell cycle entry would be greatly beneficial in the treatment of this still uncurable disease. Berberine (BRB), an isoquinoline quaternary alkaloid isolated from medicinal plants that has a long history of use in old Chinese medicine, is currently used as a dietary nutritional supplement to treat a variety of different conditions, which include metabolic and cardiovascular disorders, type 2 diabetes, atherosclerosis, senile osteoporosis, Alzheimer's disease, hypercholesterolemia, and diabetes-induced renal inflammation. In addition to the reported beneficial effects in different fields of medicine, BRB has recently received attention for its potential antitumor activity. We wondered whether BRB has apoptotic and anti-proliferative activity on leukemic cells derived from CLL patients. BRB was administered in vitro either to quiescent cells or during CLL cell activation stimuli, provided by classical co-culturing with CD40L-expressing fibroblasts. At doses (in the microM range), that were totally ineffective on normal lymphocytes, BRB induces apoptosis of quiescent CLL cells and inhibition of cell cycle entry when CLL are stimulated by CD40-CD40L ligation. This cytostatic effect is accompanied by decreased expression of survival- and proliferation-associated proteins, adhesion- and homing-molecules. Importantly, the activity of signaling pathways specifically involved in CLL disease progression such as STAT3/NF-kB, were remarkably down-regulated. In drug combination experiments, BRB lowered the apoptotic threshold of classical and novel antitumor molecules. Our results indicate that, while CLL cells after stimulation are in the process of building their full survival and cycling armamentarium, the presence of BRB may affect this process.

Key words

Apoptosis, cell cycle, chronic lymphocytic leukemia.