Phytochemical Modulation of Apoptosis and Autophagy: Strategies to Overcome Chemoresistance in Leukemic Stem Cells in the Bone Marrow Microenvironment.

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Abstract

Advances in scientific research and targeted treatment regimes have improved survival rates for many cancers over the past few decades. However, for some types of leukemia, including acute lymphoblastic and acute myeloid leukemia, mortality rates have continued to rise, with chemoresistance in leukemic stem cells (LSCs) being a major contributing factor. Most cancer drug therapies act by inducing apoptosis in dividing cells but are ineffective in targeting quiescent LSCs. Niches in the bone marrow, known as leukemic niches, behave as "sanctuaries" where LSCs acquire drug resistance. This review explores the role of the bone marrow environment in the maintenance of LSCs and its contribution to chemoresistance and considers current research on the potential use of phytochemicals to overcome chemoresistance through the modulation of signaling pathways involved in the survival and death of leukemic clonal cells and/or leukemic stem cells. Phytochemicals from traditional Chinese medicine, namely baicalein, chrysin, wogonin (constituents of Scutellaria baicalensis; huáng qín;), curcumin (a constituent of Curcuma longa, jiāng huáng,), and resveratrol (a constituent of Polygonum cuspidatum; hǔ zhàng,) have been shown to induce apoptosis in leukemic cell lines, with curcumin and resveratrol also causing cell death via the induction of autophagy (a nonapoptotic pathway). In order to be effective in eliminating LSCs, it is important to target signaling pathways (such as Wnt/β-catenin, Notch, and Hedgehog). Resveratrol has been reported to induce apoptosis in leukemic cells through the inhibition of the Notch and Sonic hedgehog signaling pathways, therefore showing potential to affect LSCs. While these findings are of interest, there is a lack of reported research on the modulatory effect of phytochemicals on the autophagic cell death pathway in leukemia, and on the signaling pathways involved in the maintenance of LSCs, highlighting the need for further work in these areas.