

Induction of S phase cell arrest and caspase activation by polysaccharide peptide isolated from *Coriolus versicolor* enhanced the cell cycle dependent activity and apoptotic cell death of doxorubicin and etoposide, but not cytarabine in HL-60 cells.

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Activation of the cell death program (apoptosis) is a strategy for the treatment of human cancer, and unfortunately a large number of drugs identified as cell cycle-specific agents for killing cancer cells are also toxic to normal cells. The present study demonstrates that the polysaccharide peptide (PSP) extracted from the Chinese medicinal mushroom, *Coriolus versicolor*, used in combination therapy in China, has the ability to lower the cytotoxicity of certain anti-leukemic drugs via their interaction with cell cycle-dependent and apoptotic pathways. Flow cytometry analysis demonstrated that pre-treatment of PSP (25-100 microg/ml) dose-dependently enhanced the cell cycle perturbation and apoptotic activity of doxorubicin (Doxo) and etoposide (VP-16), but not cytarabine (Ara-C) in human promyelocytic leukemia HL-60 cells. The antagonistic result from combined treatment with Ara-C and PSP may be caused by the removal of HL-60 cells in the G1-S boundary by PSP before exposure to Ara-C. A negative correlation between the increase in apoptotic cell population (pre-G1 peak) with the S-phase cell population expression ($R^2=0.998$), the expression of cyclin E expression ($R^2=0.872$) and caspase 3 activity ($R^2=0.997$) suggests that PSP enhanced the apoptotic machinery of Doxo and VP-16 in a cell cycle-dependent manner and is mediated, at least in part, by the PSP-mediated modulation of the regulatory checkpoint cyclin E and caspase 3. This study is the first to describe the cell cycle mechanistic action of PSP and its interaction with other anticancer agents. Our data support the potential development of PSP as an adjuvant for leukemia treatment, but also imply the importance of understanding its interaction with individual anticancer agents.