Asparagine synthetase as a causal, predictive biomarker for L-asparaginase activity in ovarian cancer cells.

Abstract:
L-Asparaginase (l-ASP), a bacterial enzyme used since the 1970s to treat acute lymphoblastic leukemia, selectively starves cells that cannot synthesize sufficient asparagine for their own needs. Molecular profiling of the NCI-60 cancer cell lines using five different microarray platforms showed strong negative correlations of asparagine synthetase (ASNS) expression and DNA copy number with sensitivity to l-ASP in the leukemia and ovarian cancer cell subsets. To assess whether the ovarian relationship is causal, we used RNA interference to silence ASNS in three ovarian lines and observed 4- to 5-fold potentiation of sensitivity to l-ASP with two of the lines. For OVCAR-8, the line that expresses the least ASNS, the potentiation was >500-fold. Significantly, that potentiation was >700-fold in the multidrug-resistant derivative OVCAR-8/ADR, showing that the causal relationship between ASNS expression and l-ASP activity survives development of classical multidrug resistance. Tissue microarrays confirmed low ASNS expression in a subset of clinical ovarian cancers as well as other tumor types. Overall, this pharmacogenomic/pharmacoproteomic study suggests the use of l-ASP for treatment of a subset of ovarian cancer.
cancers (and perhaps other tumor types), with ASNS as a biomarker for patient selection.