

Mislocation of APAFI as a Novel Diagnostic and Prognostic Marker for Refractory Diffuse B-Cell Lymphoma?

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Abstract

Resistance to chemotherapy remains a serious challenge in the clinical management of diffuse B-cell lymphomas, despite aggressive chemotherapy such as CHOP and monoclonal CD20. We previously reported that sequestration of Apaf-1 to membrane lipid rafts was responsible for apoptosis resistance in B-cell lymphoma cell lines¹. Here, we extended our studies to clinical biopsies from lymphoma patients in order to investigate if the resistance to drug-induced apoptosis was, indeed, a function of Apaf-1 mislocalization. Whereas most T-cell lymphomas (as well as cells from patients with reactive lymphadenopathy) were sensitive to apoptotic stimuli, B-cell lymphomas exhibited strong resistance. We then investigated the expression of Apaf-1 and its intracellular localization using conventional biochemical approaches as well as imaging, including laser scanning cytometry. We observed normal cytosolic localization of Apaf-1 expression in T-cell lymphoma samples as well as in cells derived from reactive lymphadenopathy biopsies. In contrast, whereas cytosolic Apaf-1 expression was significantly lower or absent in almost all B-cell lymphomas, increased localization of the protein was detected in membrane lipid rafts. Interestingly, the resistance of B-cell lymphomas to apoptotic execution was significantly bypassed upon incubation of cells with pharmacological agents that facilitated the dissociation of Apaf-1 from the lipid rafts to the cytosol. Taken together, our results implicate Apaf-1 mislocalization as a potential diagnostic marker for B-cell lymphomas as well as a predictor of response to therapeutic management.

1 Sun, Y., Orrenius, S., Pervaiz, S., Bengt, F. Plasma membrane sequestration of apoptosis protease activating factor-1 in human B lymphoma cells: a novel mechanism of chemoresistance. Blood, 105(10):4070-4077,2005.