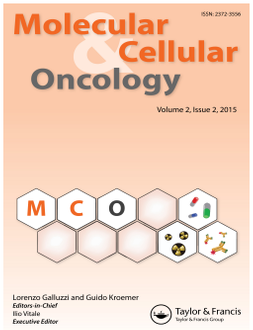

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Redox regulation of Smac mimetic-induced cell death

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Cell death and survival programs are controlled by the cellular redox state, which is typically dysregulated during oncogenesis. A recent study reports that the inhibition of antioxidant defenses resulting from glutathione depletion can prime acute lymphoblastic leukemia cells for death induced by Smac mimetics.

Keywords: apoptosis, Smac, leukemia, redox, cell death

Abbreviations: ALL, acute lymphoblastic leukemia; cIAP, cellular IAP; GPX4, GHS peroxidase; GSH, glutathione; IAP, inhibitor of apoptosis; NF-κB nuclear factor-kappa B; ROS, reactive oxygen species; XIAP, x-linked IAP.

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Children with high-risk acute lymphoblastic leukemia (ALL) still have a dismal prognosis. This emphasizes the urgent medical need to develop novel therapeutic strategies. Since resistance to treatment may be caused by the evasion of cell death, reactivation of cell death programs might pave the way to more effective treatment options.[1] Evasion of apoptosis may be caused by aberrantly high expression levels of antiapoptotic proteins, such as members of the inhibitor of apoptosis (IAP) protein family.[2] Indeed, high expression levels of x-linked IAP (XIAP) protein and cellular IAP (cIAP)1 have been linked to poor outcome in pediatric ALL.[3] One strategy to antagonize IAP proteins in human cancers involves the use of small-molecule inhibitors of IAP proteins, including Smac mimetics. Smac mimetics mimic the endogenous antagonist of IAP proteins Smac, a mitochondrial intermembrane protein that is released into the cytosol upon the induction of apoptosis.[2] Smac promotes the induction of apoptosis by binding to and antagonizing IAP proteins such as XIAP and cIAP, thereby promoting caspase activation as well as nuclear factor-kappa B (NF-κB) activity.[2] Increasing evidence suggests that the potential of Smac mimetics as novel anticancer therapeutics may in particular reside in their use in rational combination therapies, as only a small percentage of human cancers turned out to be susceptible to treatment with Smac mimetics alone.[2]

A recent study provides new insights into redox regulation of Smac mimetic-mediated cell death. Schoeneberger et al. report that inhibition of one of the key antioxidant defense pathways via depletion of glutathione (GSH) using buthionine sulfoximine (BSO) renders ALL cells sensitive to apoptosis induced by the Smac mimetic BV6.[4] This synergistic induction of apoptosis by combined treatment with BV6 and BSO occurs not only in ALL cell lines, but also in patient-derived primary leukemic samples, thus emphasizing the clinical relevance of this discovery. In contrast, combination treatment with BV6 and BSO failed to cooperate in the activation of cell death pathways in normal lymphohematopoietic cells derived from healthy donors, which points to at least some level of tumor selectivity. In mechanistic terms, BV6 and BSO act in concert to trigger the generation of reactive oxygen species (ROS). This BV6/BSO-stimulated ROS production is critically required for cell death induction, since different ROS scavengers protected ALL cells from cell death in response to combination treatment. Intriguingly, lipid peroxidation most likely caused by ROS production in the vicinity of lipid membranes turned out to be crucial for BV6/BSO-induced cell death. This conclusion is supported by pharmacologic and genetic evidence, as inhibition of lipid peroxidation by α-tocopherol or by overexpression of GHS peroxidase 4 (GPX4) can rescue BV6/BSO-induced cell death. GPX4 is the only GPX that reduces hydroperoxides within membranes.[5] The important role of lipid peroxidation is further underscored by experiments showing that RNA interference-mediated silencing of GPX4 increases lipid peroxidation in parallel with cell death upon treatment with BV6 and BSO.

Whereas GPX4 has recently been described to play an important role in the regulation of ferroptosis, an iron-dependent mode of non-apoptotic cell death,[6] BV6/BSO-triggered cell death cannot be inhibited by iron-chelating compounds.

The discovery of redox regulation of Smac mimetic-induced cell death has important implications for the design of therapeutic strategies using Smac mimetics in pediatric ALL. It is important to note that the GSH-depleting agent BSO is already being evaluated in clinical trials, including clinical studies in pediatric patients. This emphasizes the feasibility of translating this novel combination approach into clinical application. Since redox homeostasis has been described to be dysregulated in acute leukemia with a concomitant increase in both ROS levels and antioxidant defense mechanisms, the use of GSH-depleting agents might provide a tool to target this survival strategy in ALL cells. In conclusion, regulation of Smac mimetic-mediated cell death in ALL through the cellular redox status may open novel perspectives for the use of Smac mimetics as cancer therapeutics.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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