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Cytotoxic agent, oxidative stress, N-acetylcysteine, cell death protection and overlooked chemistry behind

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Statement of the Problem: Many cytotoxic agents induce cell death that is accompanied by Reactive Oxygen Species (ROS) production and by Glutathione (GSH) depletion. Not surprisingly, N-Acetylcysteine (NAC), well known antioxidant and precursor of GSH synthesis, prevents the ROS production, restores GSH level and prevents cells from death. Such effect of NAC is usually used as corroborative evidence that, cell death induced by studied cytotoxic agent is mediated by ROS production and/or by GSH depletion. Detailed analysis of many experimental systems, however, shows that such simple interpretation of results might be misleading. The purpose of this study is to describe the general experimental approach as to how to avoid misinterpretation of the results.

Methodology: A detailed LC/MS/MS analysis of the possible interactions between studied cytotoxic agent and NAC within cells and in the growth medium was made.

Findings: We studied various compounds that are known to induce ROS production and/or GSH depletion prior to cell death induction and whose cytotoxicity can be abrogated by NAC. LC/MS/MS analysis revealed that NAC covalently bound to these compounds usually by non-enzymatic reaction and converted them into nontoxic compounds: Agent-NAC or agent-2NAC.

Conclusion & Significance: NAC is a reactive compound that may directly interact with the studied cytotoxic agent, while converting it into non-cytotoxic compound covalently bound with NAC.

Recent Publications

- Mlejnek P, Dolezel P and Kosztyu P (2012) P-glycoprotein mediates resistance to A3 adenosine receptor agonist 2-chloro-N6-(3-iodobenzyl)-adenosine-5'-N-methyluronamide in human leukemia cells. *J Cell Physiol* 227: 676-685.
- Kosztyu P, Dolezel P and Mlejnek P (2013) Can P-glycoprotein mediate resistance to nilotinib in human leukaemia cells? *Pharmacol Res* 67 (1): 79-83.
- Kosztyu P, Bukvova R, Dolezel P and Mlejnek P (2014) Resistance to daunorubicin, imatinib, or nilotinib depends on expression levels of ABCB1 and ABCG2 in human leukemia cells. *Chem Biol Interact* 219: 203-210.
- Mlejnek P and Dolezel P (2014) N-acetylcysteine prevents the geldanamycin cytotoxicity by forming geldanamycin-N-acetylcysteine adduct. *Chem Biol Interact* 220: 248-254.
- Mlejnek P and Dolezel P (2015) Loss of mitochondrial transmembrane potential and glutathione depletion are not sufficient to account for induction of apoptosis by carbonyl cyanide 4-(trifluoromethoxy) phenylhydrazone in human leukemia K562 cells. *Chem Biol Interact*. 239: 100-110.

Biography

Petr Mlejnek is currently working as an Associate Professor in Biology and Head of the Department of Anatomy at the Palacky University in Olomouc, Czech Republic. He completed his Master's in Biochemistry from the University of J E Purkyne in Brno, Czech Republic and obtained his PhD degree in Biophysics from the Institute of Biophysics Academy of Science of the Czech Republic in Brno, Czech Republic. He is a member of Scandinavian Society for Cell Toxicology and International Society for the Study of Xenobiotics. Currently, he and his research group are focused on the study of mechanisms of cell death in cancer cells and mechanisms of multidrug resistance in cancer cells.

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