Oxaliplatin-dependent apoptosis: different apoptotic process in primary astrocytes vs colorectal cancer cells

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Oxaliplatin is a platinum-organic drug with anti-neoplastic properties used for colon-rectal cancer. In respect to other platinum derivates, oxaliplatin induced only a mild hematological and gastrointestinal damage. Its limiting side effects are the neurotoxicity and the subsequent nerve hyperexcitability whom result in a neuropathic syndrome. In a rat model of oxaliplatin-induced neuropathy we underlined a significant oxidative stress induced by the chemotherapic agent. Silibinin and α-tocopherol, two well known natural antioxidants, prevent the oxidative damage and, at same time, reduced neuropathic pain [1].

Aimed to deep inside the mechanism of oxaliplatin neurotoxicity we developed a cellular model using rat astrocytes, glia cells significantly activated in neuropathic rats repeatedly treated with oxaliplatin [2]. In cell cultures, oxaliplatin-evoked redox unbalance led to the activation of the apoptotic process evaluated by caspase-3 activity, a central effector of the controlled cell death. 10 μM silibinin and α-tocopherol protected astrocytes from oxaliplatin-induced caspase-3 activation. To evaluate the safety of these compounds towards the oxaliplatin anti-tumoral efficacy, apoptosis signal was analyzed in HT-29, a human colorectal cancer cell line. Interestingly, the antioxidant compounds were completely inactive against oxaliplatin-dependent apoptosis in HT-29. These evidences suggested different mechanisms by which oxaliplatin induces apoptosis in tumoral rather normal cells. Therefore, in the present study, we compared the intrinsic (mitochondrial) and the extrinsic apoptotic pathway activation in astrocytes and HT-29 cells after oxaliplatin treatment. In astrocyte cultures, after 8h incubation, 100 μM oxaliplatin induces a cytosolic release of cytochrome C by about 130%. This data is in line with the reduction (60%) of the expression of the anti-apoptotic protein Bcl-2. On the contrary, these parameters are unaltered in the HT-29 cultures where oxaliplatin incubation (100 μM; 8h) induced an increase of caspase-8 activity (80%), one of the main effector of the extrinsic pathway. Moreover, in HT-29, after oxaliplatin treatment we observed an increase (70%) of Bid expression, a protein activated by caspase-8. On the contrary Bid is not detectable in astrocyte cultures. Taken together these data suggest that oxaliplatin treatment induces the intrinsic apoptosis activation in astrocytes normal cells. In tumoral cells, the extrinsic apoptotic pathway is prevailing. In this perspective, new agents candidate to treat oxaliplatin neuropathy, should possess protective properties against mithocondrial disfunctions. On the other hand, the chemotherapy anticancer efficacy could be maintained preserving the extrinsic apoptotic pathway activation.

Reference:

1. Di Cesare Mannelli et al. *Oxaliplatin-induced neuropathy: Oxidative stress as pathological mechanism. Protective effect of silibinin*. The Journal of Pain, Vol 13, No 3 (March), 2012 Mar;13(3):276-84
2. Di Cesare Mannelli et al. *Oxaliplatin-induced oxidative stress in nervous-derived cellular models. Could it correlate with in vivo neuropathy?*. Free Radic Biol Med. 2013 Mar 30 31; 61C:143-150