# Resveratrol Effects on SOD2

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The adaptive response has been routinely defined by the use of a very low dose of radiation to stimulate cellular processes that result in an enhanced resistance to a second but larger challenge dose of radiation. We have observed that other agents such as thiol-containing drugs also have the ability to affect cellular processes that result in an acquired or adaptive response reflective of increased radiation resistance. Presumably, both low dose radiation and thiol-containing drugs induce a shared pathway that leads to elevated manganese superoxide dismutase (SOD2) levels which accounts for the enhanced cellular resistance to ionizing radiation exposure. We have expanded our studies to include another class of agents, represented by resveratrol (3,4',5-trihydroxystilbene), that are known to affect SOD2 activity. Resveratrol has been shown to induce SOD2 under specific treatment conditions. Studies with resveratrol typically involve continuous exposure of cells for several days before determining the effectiveness of the agent as a radioprotector. In studies reported here, SA-NH murine sarcoma tumor cells established for growth in culture were exposed to a single dose of 50μM resveratrol and analyzed for SOD2 activity from 2 h to 28 h post-treatment. Thiols, including amifostine (S-2-[3-aminopropylamino]ethylphosphorothioic acid) mesna (sodium-2-mercaptoethanesulfonate), NAC (N-acetyl-L-cysteine) and captopril ([S]-1-[3-mercapto-2-methyl-1-oxo-propyl]-L-proline), are effective inducers of SOD2. While thiols induce SOD2 via the NFκB signaling pathway, resveratrol acts through the FOXO3a pathway. Results from resveratrol studies show cellular induction of SOD2 peaking within 4-6 h after exposure. In contrast, WR1065, the active form of amifostine, shows peak SOD2 levels at 24 h post exposure. Both agents showed similar levels of SOD2 activity at the time periods corresponding to their respective maximal activities. Cell survival after exposure to 2 Gy x-rays confirms the protective effects of resveratrol and WR1065 at their respective peak levels of SOD2. Treating cells to both resveratrol and WR1065 before exposure to a single dose of 2 Gy x-rays at 4 h, 6 h, or 24 h post-treatment showed radioprotection similar to cells treated to either agent alone. In addition, challenging cells with 2 Gy x-rays after exposure to resveratrol and WR1065 at their peak levels of SOD2 (6 h and 24 h respectively) did not show additional radioprotection compared to each agent administered alone. Therefore, in preliminary studies, it appears that the radioprotective effects of resveratrol and WR1065 are not additive but result in a more prolonged elevation of SOD2 and radioresistance.

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