NEW HORIZONS

Oxidative Stress : A Novel Strategy in Cancer Treatment

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Introduction

There is an equilibrium between a free radical (FR)/ reactive oxygen species (ROS) formation and endogenous antioxidant defense mechanisms, but if this balance is disturbed, it can produce oxidative stress. This state of oxidative stress can result in injury to all the important cellular components like proteins, DNA and membrane lipids which can cause cell death. In recent years, increasing experimental and clinical data has provided compelling evidences for the involvement of oxidative stress in large number of pathological states including carcinogenesis (1,2). Oxidative stress however, is not always detrimental. Selective oxidative stress sometimes is desirable and can be utilized therapeutically also. There are numerous drugs which are known to act by the mechanism of oxidative stress and can be utilized therapeutically like chloroquin, quinine, mefloquine, primaquin, artemisinin (3) and ciprofloxacin (4) etc. Recently, new therapeutic strategies that take advantage of increased reactive oxygen species or inhibition of endogenous antioxidant defense, hence producing a state of oxidative stress selectively in cancer cells have gained importance.

Potential anticancer agents acting by the mechanism of oxidative stress.

Alkylating agents and radioactive isotopes are well known to kill cancer cells by the mechanism of oxidative stress (3). *Hileman et al* proposed a hypothesis that inhibition of superoxide dismutase (SOD) may provide a novel way to kill cancer cells. Since, SOD is critical enzyme responsible for the elimination of superoxide radicals and is considered to be a key antioxidant in aerobic cells,therefore, deficiency in SOD or inhibition of the enzyme activity may cause severe accumulation of superoxide free radicals in the cells and can result irreversible cellular injury and ultimately result in cancer cell death (5). Studies suggest that, by interfering with mitochondrial electron transport chain and increasing the production of superoxide free radicals in human leukemic cells are the novel mechanisms to enhance apoptosis, induced by a clinically active antileukemic agent, arsenic trioxide-AS_2O_3 (6). This agent has been also suggested to induce apoptosis of esophageal cancer cells (7). Arsenic trioxide with L-buthionine-sulfoxine could be promising new drug against not only in the treatment of leukemia but also solid tumors. L-buthionine-sulfoxine, which inhibits a critical step in glutathione synthesis effectively enhance, in vitro, growth inhibitory effects of arsenic trioxide on all the eleven investigated cancer cell lines arising from prostate, breast, lung, colon, cervix, bladder and kidney cancers etc (8).

Similarly, docosahexaenoic acid, a polyunsaturated fatty acid enhances arsenic trioxide mediated apoptosis in arsenic trioxide resistant HL–60 cancer cells and thereby, it may sensitize this tumor cell effectively (9). 2–methoxyestradial (2-ME), a new anticancer agent currently in clinical trials, has been demonstrated to inhibit superoxide dismutase and to induce apoptosis in leukemia cells through a free radical mediated mechanism without exhibiting significant cytotoxicity in normal lymphocytes (10). Further, more it was also suggested that intrinsic oxidative stress in the cancer cell is a biochemical basis for therapeutic selectivity shown by 2–methoxyestradial (11). Catalase enzyme, which is very important to catabolize hydrogen peroxide is inhibited by ceramide and thereby it increases oxidative stress and induces HL–60 cancer cell apoptosis (12). N–(4-Hydroxyphenyl) retinamide (4-HPR) induces lymphoblastic leukemia cell death by generation of reactive oxygen species (13) and altholactone, a novel styryl–lactone induces apoptosis via oxidative stress in human HL–60 leukemia cells (14).

Neural crest tumors of childhood are particularly resistant to apoptosis induced by chemotheraupetic

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agents. Recently, Schor *et al* have designed and tested, preclinical model system approach to this problem. This approach includes adjunctive use of oxygen radical–generating neurotransmitter analog (6–hydroxydopamine) taken up by these neural crest tumor cells with scavenging agent [tempol (4–hydroxy–2, 2, 6, 6–tetramethyl pepridine–N–oxyl) which is selective for normal neural crest and the use of reduction dependant prodrug of apoptosis–inducing agent (neocarzinostatin). This strategy can induce apoptosis even in resistant neoplasms (15).

Even diethyldithiocarbamate (DDTC) induced cytotoxicity via oxidative shift in the intracellular redox state accompany the activation of endonuclease through apoptosis in leukemia cell lines (16). Another important potential drug in this category is sodium selenite. It can induce apoptosis of NB4 cells and would possibly have promising role in treatment of malignancy. The main mechanism of action might be related to oxidative stress induced by sodium selenite thereby leading to induction of apoptosis in NB4 cells (17). Sodium selenite induce overt production of various reactive oxygen species by producing disturbance in mitochondrial transmembrane and decreasing intracellular glutathione, an endogenous enzymatic defense (17,18). This agent along with all–transretinoic acid in low doses can very effectively produce apoptosis in NB4 cancer cells (19). All transretonoic acid also induce apoptosis in acute promyelocytic NB4 cell when combined with isoquinolinediol, a poly (ADP-ribose) polymerase inhibitor (20). Similarly, it is also being suggested that tributyrin a potential anticancer drug can promote apoptosis of promyelocytic leumkemia cells (21). The involvement of oxidative stress in tumor necrosis factor (TNF–á) related apoptosis in Hela cancer cells has also been suggested recently (22).

Some ROS may react with DNA, and in few cases may abstract an electron from the double helix, leading to long range electron transfer (ET) reactions. Thus, the DNA of living cells may be in a continuous state of ET. Acridine-based anticancer drugs, which bind to DNA by intercalation, might either donate electrons to, or accept electrons from, the double helix, thus actively participating in ET reactions. Particularly two acridine-based drugs have been tested against human cancer in the clinic. Amsacrine is a 9-anilinoacridine derivative that appears to act as an electron donor in ET reactions on DNA, while N-[2-(dimethylamino) ethyl]acridine-4-carboxamide (DACA) may act as an electron acceptor. Such reactions may make important contributions to the antitumor activity of these drugs (23).

Calcitriol, the hormonal form of vitamin D, enhances the anticancer activity of the immune cytokine tumor necrosis factor, interleukin 1 and interleukin 6 in human breast and renal cell carcinoma cells without affecting the cytotoxic action of interferon-alpha or killer lymphocytes. It also enhances cytotoxicity induced by the anticancer drug doxorubicin, by the redox cycling quinone menadione, and by the reactive oxygen species hydrogen peroxide. The synergistic interaction was accompanied by increased oxidative stress, as manifested by glutathione depletion and was abolished by exposure to the thiol antioxidant N-acetylcysteine. The hormone on its own brought about an increase in the cellular redox state as reflected in the ratio between oxidized and reduced glutathione and glyceraldehyde-3-phosphate dehydrogenase, and a reduction in the expression of the antioxidant enzyme Cu/Zn superoxide dismutase (24).

Iron chelators can deplete iron or cause oxidative stress in the tumor due to redox perturbations in its environment. They have been tested for their anti-tumor activity in cell culture experiments, animal models and human clinical trials. Examples of iron chelators that have shown promising anti-tumor activity (in various stages of development) include heterocyclic carboxaldehyde thiosemicarbazones, analogs of pyridoxal isonicotinoyl hydrazone, tachpyridine, O-trensox, desferrithiocin, and other natural and synthetic chelators. Apart from their use as single agents, chelators may also synergize with other anti-cancer therapies (25).

Complex/dual role of oxidative stress in carcinogenesis

Many recent studies have proved the role of oxidative stress in carcinogenesis (26,27). The role of vitamin antioxidants in reducing the risk of various cancers by suppressing the state of oxidative stress have been documented recently (28,29). The present review suggests that oxidative stress is not always detrimental, as it can be beneficial in cancers sometimes. Hence, oxidative stress can act as a double way sword in malignant states.

Conclusion

Oxidative stress sometimes can be utilized therapeutically. Potential anticancer drugs acting by this mechanism may prove novel in future. However ,there is a concern for selective production of oxidative stress in cancer cells only, without exhibiting significant cytotoxicity in the normal cells. Moreover, there is a need of conducting larger, adequately powered clinical trials to prove therapeutic efficacy and selectivity of these potential anticancer agents acting by oxidative stress mechanisms.

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